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(54) Title: SUBTYPE-SELECTIVE NMDA RECEPTOR LIGANDS AND THE USE THEREOF

(57) Abstract

The invention relates to subtype-selective NMDA receptor ligands and the use thereof for treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Down's syndrome, treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, treating anxiety, psychosis, convulsions, aminoglycoside antibiotics-induced hearing loss, migraine headache, chronic pain, Parkinson's disease, glaucoma, CMV retinitis, urinary incontinence, opioid tolerance or withdrawal, and inducing anesthesia, as well as for enhancing cognition.

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TITLE

Subtype-Selective NMDA Receptor Ligands and the Use Thereof

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is related to 2-substituted piperidine analogs. The analogs are selectively active as antagonists of N-methyl-D-aspartate (NMDA) receptor subtypes. The invention is also directed to the use of 2-substituted piperidine analogs as neuroprotective agents for treating conditions such as stroke, cerebral ischemia, central nervous system trauma, hypoglycemia, anxiety, convulsions, aminoglycoside antibiotics-induced hearing loss, migraine headaches, chronic pain, glaucoma, CMV retinitis, psychosis, urinary incontinence, opioid tolerance or withdrawal, or neuro-degenerative disorders such as lathyrism, Alzheimer's Disease, Parkinsonism and Huntington's Disease.

Related Background Art

Excessive excitation by neurotransmitters can cause the degeneration and death of neurons. It is believed that this degeneration is in part mediated by the excitotoxic actions of the excitatory amino acids (EAA)

glutamate and aspartate at the N-methyl-D-Aspartate (NMDA) receptor. This excitotoxic action is considered responsible for the loss of neurons in cerebrovascular disorders such as cerebral ischemia or cerebral infarction resulting from a range of conditions, such as thromboembolic or hemorrhagic stroke, cerebral vasospasms, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery and cerebral trauma, as well as lathyrism, Alzheimer's Disease, Parkinson's Disease and Huntington's Disease.

Excitatory amino acid receptor antagonists that block NMDA receptors are recognized for usefulness in the treatment of disorders. NMDA receptors are intimately involved in the phenomenon of excitotoxicity, which may be a critical determinant of outcome of several neurological disorders. Disorders known to be responsive to blockade of the NMDA receptor include acute cerebral ischemia (stroke or cerebral trauma, for example), muscular spasm, convulsive disorders, neuropathic pain and anxiety, and may be a significant causal factor in chronic neurodegenerative disorders such as Parkinson's disease [T. Klockgether, L. Turski, Ann. Neurol. 34, 585-593 (1993)], human immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral sclerosis (ALS), Alzheimer's disease [P.T. Francis, N.R. Sims, A.W. Procter, D.M. Bowen, J. Neurochem. 60 (5), 1589-1604 (1993)] and Huntington's disease. [See S. Lipton, TINS 16 (12), 527-532 (1993); S.A. Lipton, P.A. Rosenberg, New Eng. J. Med. 330 (9), 613-622 (1994); and C.F. Bigge, Biochem. Pharmacol. 45, 1547-1561 (1993) and references cited therein.]. NMDA receptor antagonists may also be used to prevent tolerance to opiate analgesia or to help control withdrawal symptoms from addictive drugs (Eur. Pat. Appl. 488,959A).

U.S. Patent 5,352,683, discloses the treatment of chronic pain with a compound with is an antagonist of the NMDA receptor.

U.S. Patent 4,902,695, discloses certain competitive NMDA antagonists that are useful for the treatment of neurological disorders, including epilepsy, stroke, anxiety, cerebral ischemia, muscular spasms, and neurodegenerative diseases such as Alzheimer's disease and Huntington's disease.

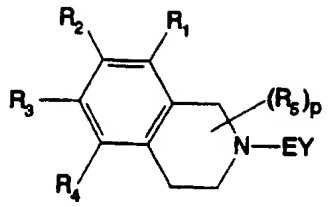
U.S. Patent 5,192,751 discloses a method of treating urinary incontinence in a mammal which comprises administering an effective amount of a competitive NMDA antagonist.

Evidence indicates that the NMDA receptor comprises a class of such receptors with different subunits. Molecular cloning has revealed the existence of at least five subunits of the NMDA receptors designated NR1 & NR2A through 2D. It has been demonstrated that the co-expression of NR1 with one of the NR2 subunits forms a receptor with a functional ion channel. (*Ann. Rev. Neurosci.* 17:31-108(1994)). It is thought that NMDA receptors with different subunit composition generate the different NMDA receptor subtypes found in the mammalian brain.

An object of this invention is to provide novel - subtype-selective NMDA receptor ligands.

SUMMARY OF THE INVENTION

The invention relates to a subtype-selective NMDA receptor ligand having the Formula (*I*):



wherein

R_1-R_4 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, cyanamido, $N(CN)_2$, guanidino, amidino, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl (CO), or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1;

R_5 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

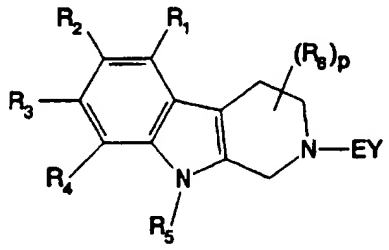
p is 0, 1, 2, or 3;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally

substituted aroyl, =Y_1, -Y_1 (which may be cis or trans, throughout) carbonylamido, hydrazino, oximo, amidino, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*II*):



wherein

R_1-R_4, E, Y and Y_1 are the same as described in formula I;

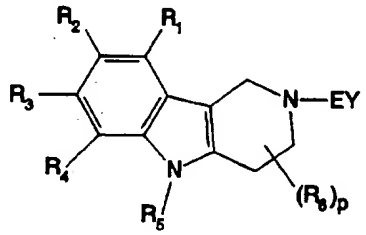
R_5 is hydrogen, lower alkyl, acyl or aryl;

p is 0, 1, 2 or 3; and

R_6 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a

heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group; and

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*IIa*):



wherein

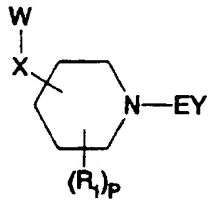
R_1-R_4, E, Y and Y_1 are the same as described in formula I;

R_5 is hydrogen, lower alkyl, acyl or aryl;

p is 0, 1, 2 or 3; and

R_6 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*III*):



wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, carbonyl, oxygen, or NR;

E is the same as described in formula I;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R; an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R is hydrogen, alkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl;

R_1 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

m is 0, 1, 2, or 3; and

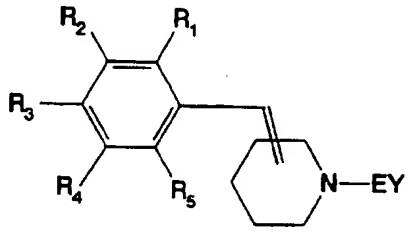
p is 0, 1, 2, 3 or 4.

with the proviso, that when W is adamantyl or when p is greater than zero, or when the piperidine is substituted in the 3-position by W-X, then Y may also be optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, $\equiv Y_1$, $=Y_1$, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted

cycloalkoxy group, amino, amido, ureido, or guanidino; wherein

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*IV*):

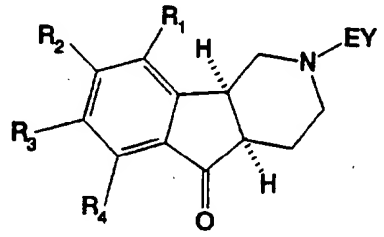


wherein

R_1-R_5 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; and

E, Y and Y^1 are the same as described in formula I.

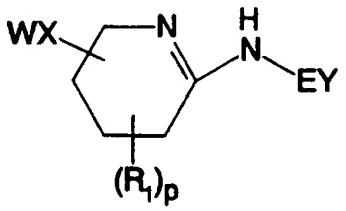
The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*V*):



wherein

R_1-R_4, E, Y and Y_1 are the same as described in formula I.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*VI*):



wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, oxygen, or NR;

E, Y and Y_1 are the same as described in formula I;

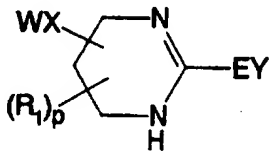
R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

m is 0, 1, 2, or 3; and

q is 0, 1 or 2.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*VII*):



wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, oxygen, or NR;

E, Y and Y_1 are the same as described in formula I;

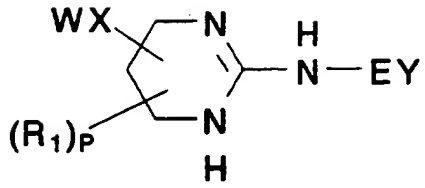
R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

m is 0, 1, 2, or 3; and

p is 0, 1 or 2.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*VIII*):



wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, oxygen, or NR;

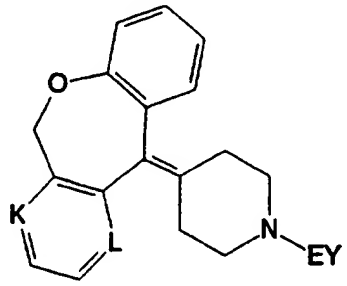
E, Y and Y_1 are the same as described in formula I;
R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

m is 0, 1, 2, or 3; and

p is 0, 1 or 2.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (***IX***):

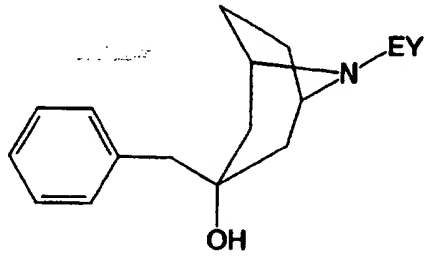


wherein

one of K and L is nitrogen and the other is CH; and

E, Y and Y_1 are the same as described in Formula I.

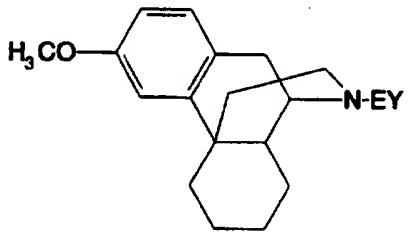
The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*X*):



wherein

E, Y and Y_1 are the same as described in formula I.

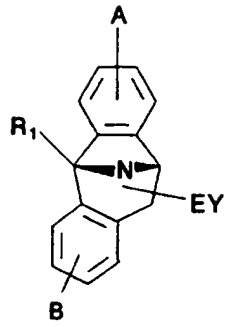
The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XI*):



wherein

E, Y and Y_1 are the same as described in formula 1.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XII*):



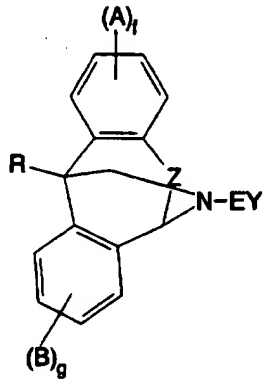
wherein

A and B are one or more substituents which are independently hydrogen, halo, alkoxy, trifluoromethylthio, cyano, carboxy or hydroxy;

R_1 is alkyl, alkenyl, aralkyl, cycloalkyl-alkyl, dialkylaminoalkyl, or hydroxyalkyl; and

E, Y and Y_1 are the same as described in formula I.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (***XIII***):



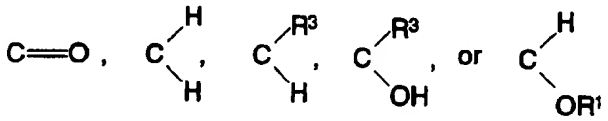
wherein

R is hydrogen, C_2-C_6 acyl, C_1-C_6 alkyl, aryl, C_1-C_6 alkoxycarbonyl, C_7-C_{10} aralkyl, C_2-C_6 alkenyl, C_3-C_{15} dialkylaminoalkyl, C_1-C_6 hydroxyalkyl, C_2-C_6 alkynyl, C_3-

C_{15} trialkylsilyl, C_4-C_{10} alkylcycloalkyl, or C_3-C_6 cycloalkyl;

A and B are independently selected from the group consisting of a halogen such as chloro, fluoro, bromo, iodo, trifluoromethyl, azido, C_1-C_6 alkoxy, C_2-C_6 dialkoxymethyl, C_1-C_6 alkyl, cyano, C_3-C_{15} dialkylaminoalkyl, carboxy, carboxamido, C_1-C_6 haloalkyl, C_1-C_6 haloalkylthio, allyl, aralkyl, C_3-C_6 cycloalkyl, aroyl, aralkoxy, C_2-C_6 acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_5-C_6 heterocycloalkyl, C_1-C_6 alkylthio, C_1-C_6 alkylsulfonyl, C_1-C_6 haloalkylsulfonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 haloalkylsulfinyl, arylthio, C_1-C_6 haloalkoxy, amino, C_1-C_6 alkylamino, C_2-C_{15} dialkylamino, hydroxy, carbamoyl, C_1-C_6 N-alkylcarbamoyl, C_2-C_{15} N,N-dialkylcarbamoyl, nitro and C_2-C_{15} dialkylsulfamoyl;

Z represents a group selected from

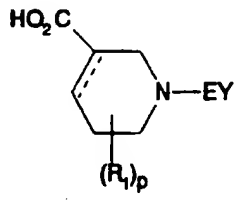


wherein R^1 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, aralkyl, C_4-C_{15} dialkylaminoalkyl, heterocycloalkyl, C_2-C_6 acyl, aroyl, or aralkanoyl, and R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, phenyl, aralkyl or C_3-C_{15} dialkylaminoalkyl; and

f and g are independently integers selected from 0 (X or Y is hydrogen, respectively), 1, 2, 3, or 4; and

E, Y and Y_1 are the same as described in formual I.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (***XIV***):



wherein

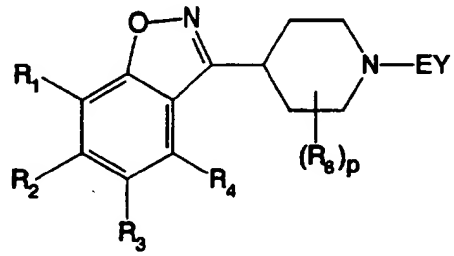
R_1 is carboxy or an alkylester or amide thereof; alkyl carboxy or an alkyl ester or amide thereof; hydroxy or hydroxymethyl group;

p is 0, 1 or 2;

the dotted line represents a single or double bond;

E, Y and Y_1 are the same as described in formula I.

The invention relates to a subtype-selective NMDA receptor ligand having the Formula (***XV***):



wherein

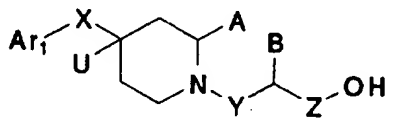
R_1-R_4, E, Y and Y_1 are the same as described in formula I;

R_6 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl,

optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group; and

p is 0, 1, 2, or 3.

The invention relates to a subtype-selective NMDA receptor ligand having the Formula (**XVI**):



wherein Ar_1 is optionally substituted aryl or optionally substituted heteroaryl;

X is O, NR_1 or $(CH_2)_n$ wherein n is 0, 1, 2, 3 or 4 and R_1 is hydrogen or a lower alkyl group having 1 to 6 carbon atoms;

U is hydroxy or hydrogen;

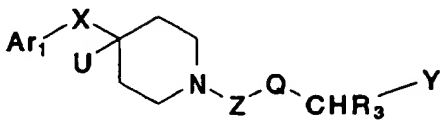
Y is $(CH_2)_m$ wherein m is 1,2 or 3;

Z is $(CHR_2)_z$ wherein z is 0, 1, 2, 3 or 4 and R_2 is hydroxy, hydrogen or a lower alkyl group having 1 to 6 carbon atoms; and

A and B are each hydrogen or together are $(CH_2)_w$ wherein w is 0, 1, 2, 3 or 4.

Preferred substituents of Ar_1 include, for example, hydrogen, alkyl, a halogenated alkyl group such as a trifluoromethyl group, halogen, nitro, aryl, aralkyl, amino, a lower alkyl amino group or a lower alkoxy group.

The invention relates to a subtype-selective NMDA receptor ligand having the Formula (**XVII**):



wherein

Ar_1 is optionally substituted aryl or optionally substituted heteroaryl;

X is O, NR_1 or $(CH_2)_n$ wherein n is 0, 1, 2, 3 or 4 and R_1 is hydrogen or a lower alkyl group having 1 to 6 carbon atoms;

U is hydroxy or hydrogen;

Z is $(CHR_2)_z$ wherein z is 0, 1, 2, 3 or 4 and R_2 is hydroxy, hydrogen or a lower alkyl group having 1 to 6 carbon atoms;

Q is -CH=CH- or -C≡C-;

R_3 is hydrogen, hydroxy or hydroxy substituted lower alkyl having 1 to 6 carbon atoms; and

Y is hydrogen, hydroxy, optionally substituted aryl or optionally substituted heteroaryl.

Preferred substituents of the aryl and heteroaryl groups include, for example, hydrogen, alkyl, a halogenated alkyl group such as a trifluoromethyl group, halogen, nitro, aryl, aralkyl, amino, a lower alkyl amino group or a lower alkoxy group.

The invention also relates to the quaternary ammonium salts of any one of the compounds above obtained by reacting the compound with a lower alkyl halide, preferable, methyl iodide or methyl sulfate.

The invention also relates to a method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Down's syndrome, treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, treating anxiety, psychosis, convulsions, chronic pain, glaucoma, CMV retinitis, urinary incontinence, and inducing anesthesia, as well as enhancing cognition, and preventing opiate tolerance and withdrawal symptoms, comprising administering to an animal in need of such treatment an effective amount of any one of the subtype-selective NMDA receptor ligands of the present invention, or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the discovery of new compounds which are subtype-selective ligands of the NMDA receptor. There are a number of subtypes of the NMDA receptor including NR1A/2A, NR1A/2B, NR1A/2C and NR1A/2D. The discovery of ligands which are selective for one or more of these subtypes allows for the treatment of various conditions mediated through binding to the NMDA receptor, while minimizing unwanted side effects.

Electrophysiological assays may be utilized to characterize the actions of potential subtype-selective

ligands at NMDA receptors expressed in *Xenopus* oocytes. The ligand may be assayed at the different subunit combinations of cloned rat NMDA receptors corresponding to the four putative NMDA receptor subtypes (Moriyoshi *et al.*, *Nature (Lond.)* *354*:31-37 (1991); Monyer *et al.*, *Science (Washington, D.C.)* *256*:1217-1221 (1992); Kutsuwada *et al.*, *Nature (Lond.)* *358*:36-41 (1992); Sugihara *et al.*, *Biochem. Biophys. Res. Comm.* *185*:826-832 (1992)).

Using fixed saturating concentrations of agonists (glutamate 100 μM, glycine 1-10 μM depending on subunit combination), the inhibitory potency of a putative subtype-selective ligand may be assayed at the NMDA receptors assembled from NR1A/2A, NR1A/2B, NR1A/2C and NR1A/2D subunit combinations.

Preferably, the subtype selective NMDA receptor ligands are limited efficacy NMDA receptor antagonists. Such limited efficacy antagonists are attractive because such drugs have built-in safety margins; no matter how high the dosage only a certain fraction of the response can be blocked. This could be particularly important for analgesic, anticonvulsant, anti-psychotic, antimigraine headache, antiparkinson's disease and antiglaucoma indications, where overdosage of full antagonists may result in sedation. It is also likely that limited efficacy NMDA receptor antagonists, particularly those showing subtype-selectivity, will not induce such profound memory deficits as full antagonists.

Certain of the subtype-selective NMDA receptor ligands are expected to be able to mediate either inhibition or potentiation of membrane current response. Which type of effect predominates appears to be dependent upon the subunit composition of the receptors and on the

structure of the molecule. The 1A/2A and 1A/2B subtypes are mainly in the forebrain. The 1A/2C and 1A/2D are mainly in the cerebellum. In addition to the potential of developing subtype-selective drugs for the treatment of diseases associated with the overstimulation of the NMDA receptor with few side effects, it is also possible to develop drugs that selectively potentiate particular subtypes of NMDA receptors present in particular parts of the brain. Such drugs could show therapeutic potential as cognitive-enhancers in treatments of neurodegenerative conditions such as Alzheimer's disease. In addition, there is a potential for developing drugs that selectively potentiate some subtypes of NMDA receptors while simultaneously having inhibitory effects at other subtypes. Such compounds could be important for adjusting imbalances in subtype activity and may have therapeutic potential as psychotropic agents.

Compounds that are useful for treating or preventing the adverse consequences of stroke, hypoglycemia, neurodegenerative disorders, anxiety, epilepsy or psychosis, or that induce analgesia, will inhibit the currents across the membranes of the oocyte expressing various subtype NMDA receptors. However, if the compound potentiates currents across the oocyte membrane, then the compound is expected to be useful in enhancing cognition.

With respect to Formulae ***I-XVII***, above:

Typical C_{6-14} aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl groups.

Typical halo groups include fluorine, chlorine, bromine and iodine.

Typical C_{1-4} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec.*-butyl, and *tert.*-butyl groups. Also contemplated is a trimethylene group substituted on two adjoining positions on any benzene ring of the compounds of the invention.

Typical C_{2-4} alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec.*-butenyl.

Typical C_{2-4} alkynyl groups include ethynyl, propynyl, butynyl, and 2-butnyyl groups.

Typical arylalkyl groups include any of the above-mentioned C_{1-4} alkyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Typical arylalkenyl groups include any of the above-mentioned C_{2-4} alkenyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Typical arylalkynyl groups include any of the above-mentioned C_{2-4} alkynyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Typical haloalkyl groups include C_{1-4} alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl and trichloromethyl groups.

Typical hydroxyalkyl groups include C_{1-4} alkyl groups substituted by hydroxy, e.g., hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups.

Typical alkoxy groups include oxygen substituted by one of the C_{1-4} alkyl groups mentioned above.

Typical alkylthio groups include sulphur substituted by one of the C_{1-4} alkyl groups mentioned above.

Typical acylamino groups include any C_{1-6} acyl (alkanoyl) substituted nitrogen, e.g., acetamido, propionamido, butanoylamido, pentanoylamido, hexanoylamido as well as aryl-substituted C_{2-6} substituted acyl groups.

Typical acyloxy groups include any C_{1-6} acyloxy groups, e.g., acetoxy, propionoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy and the like.

Typical heterocyclic groups include tetrahydrofuranyl, pyranyl, piperidinyl, piperizinyl, pyrrolidinyl, imidazolindinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl and pyrazolinyl groups.

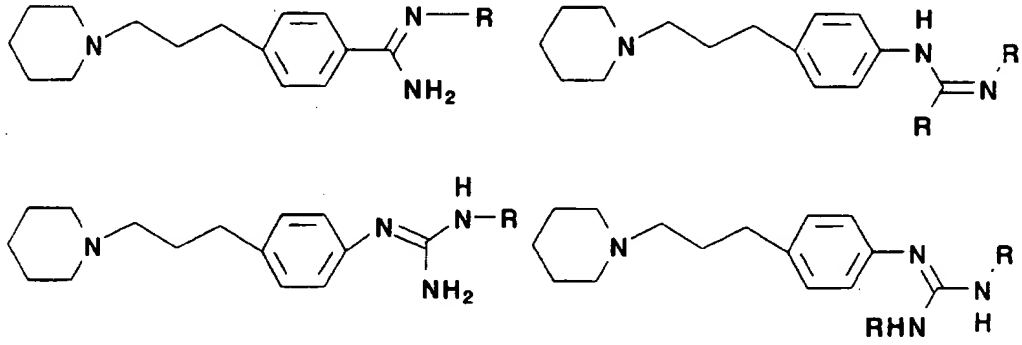
Typical heteroaryl groups include any one of the following which may be optionally substituted with one or more alkyl, halo, or hydroxy groups: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl phenoxazinyl groups, 1,4-dihydroquinoxaline-2,3-dione, 7-amino isocoumarin, pyrido[1,2-a]pyrimidin-4-one, 1,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxobenzimidazolyl, 2-oxindolyl and 4-nitrobenzofurazan.

Where the heteroaryl group contains a nitrogen atom in a ring, such nitrogen atom may be in the form of an N-oxide, e.g., a pyridyl N-oxide, pyrazinyl N-oxide, pyrimidinyl N-oxide and the like.

Typical amino groups include $-NH_2$, $-NHR^{14}$, and $-NR^{14}R^{15}$, wherein R^{14} and R^{15} are C_{1-4} alkyl groups as defined above.

Typical carbonylamido groups are carbonyl groups substituted by $-NH_2$, $-NHR^{14}$, and $-NR^{14}R^{15}$ groups as defined above.

When the group is an amidino or guanidino group, any one of the nitrogen atoms may be substituted, e.g.,



where each R is independently hydrogen, alkyl, or aryl.

Optional substituents on the aryl, aryloxy, arylthioxy, aroyl, heterocyclic, heterocycloxy, heteroaryl, heteroaryloxy, cycloalkyl, and cycloalkoxy groups listed above include any one of the typical halo, haloalkyl, aryl, fused aryl, heterocyclic, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, and alkylthiol groups mentioned above.

In the compounds having the above formulae, the group E is a linker group between the nitrogen, e.g., piperidine nitrogen, and the terminal group Y. Excluded from such Formulae are where two heteroatoms are adjacent to one another such that an unstable compound would be produced. Such adjacent heteroatoms include -O-O-, -O-S-(divalent sulfur), -N-S-(divalent sulfur), -S-O-(divalent sulfur), and -S-N-(divalent sulfur). Hydrazine groups (-N-N-) are contemplated as possible linkers. Preferably, the group E is an optionally substituted methylene linker. Most preferably, the group E is a methylene linker $(CH_2)_n$, wherein n is 1, 2, 3, 4, 5 or 6.

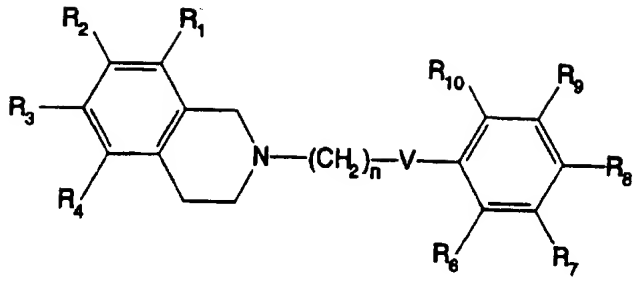
Preferably, the group Y is an N-hydroxyalkylpiperidinyl (e.g., hydroxypropyl) group, which is expected to provide a reduction in affinity to the α_1 receptor, thereby resulting in less hypotension when the compounds are administered to animals. See, Gifford, R.W. *et al.*, *Arch. Intern. Med. 153*:154-183 (1993). Alternatively, a halo group such as a *p*-chlorophenyl group may be employed to give compounds having a prolonged *in vivo* activity.

Compounds having Formula *I* may be prepared by reaction of an appropriately substituted 1,2,3,4-tetrahydroisoquinoline with a suitable electrophile in an aprotic solvent such as toluene or acetonitrile. The starting 1,2,3,4-tetrahydroisoquinoline may be prepared by the Pictet-Spenger method described in *Org. Reactions 6*:151-206 (1951). Optionally, a base such as potassium carbonate or pyridine may be added. Examples of suitable electrophiles include, for example, an alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl, or heteroaralkyl halide, sulfate, sulfonate, or isocyanate. Specific examples of such electrophiles include ethyl 3-bromoethoxyphenyl acetate, methyl 5-

bromovalerate, ethyl 4-bromobutyrate, 3-butyn-1-methanesulfate, ethyl crotonate, 1-chloro-4-phenylbutane, 3-phenoxypropyl bromide, 4-chloro-4'-fluorobutyrophenone, 4-chlorobutyrophenone, 2-phenylethyl bromide, 1-bromo-3-phenylpropane, 3-phenoxypropyl bromide, β-bromo-phenetole, 3-phenoxypropyl bromide, 3-phenylpropyl bromide, 1,3-propanesulfone, phenylisocyanate, 4-nitrophenylisocyanate, allyl iodide, bromomethylcyclopropane, 3-bromo-1-propanol, and 5-bromovaleronitrile.

A general procedure for reaction of the piperidine-containing compound with an alkyl chloride, bromide, tosylate or mesylate involves forming a mixture of a free base of the amino derivative and an alkyl chloride or bromide in toluene, acetonitrile, DMF, acetone or ethanol, in the presence of NaI. The reaction may be refluxed for 1-10 h then cooled to room temperature, filtered and washed with hexane. The filtrate is evaporated, and the residue chromatographed over silica gel to give the product. If the product is a solid, it may be crystallized, for example, from hexane or hexane-ethyl acetate. If the product is an oil, it may be dissolved in acetone and 4N HCl solution in 1,4-dioxane or concentrated HCl may be added until the mixture becomes strongly acidic (pH < 2). It may then be rota-evaporated, and co-evaporated until a solid residue is obtained. The solid may then be recrystallized from acetone to give the hydrochloride. Alternatively, the hydrobromide or other acid addition salts may be prepared by substitution of, for example, HBr or maleic acid for HCl.

Examples of compounds having Formula *I* include those having the Formula (*Ia*):



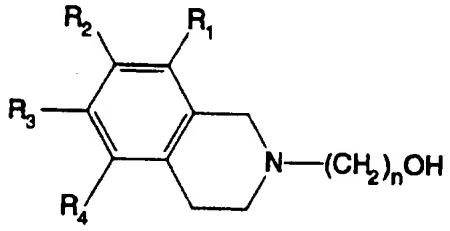
wherein

R_1-R_4 and R_6-R_{10} are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

n is 1, 2, 3, or 4; and

V is CH_2, oxygen, sulfur, or carbonyl (CO).

Other examples include those having the Formula (*Ib*):

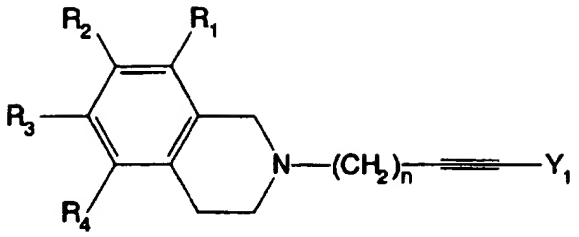


wherein

R_1-R_4 are the same as described for formula Ia; and

n is 1, 2, 3, 4, 5, or 6.

Other examples include those having the Formula (*Ic*):

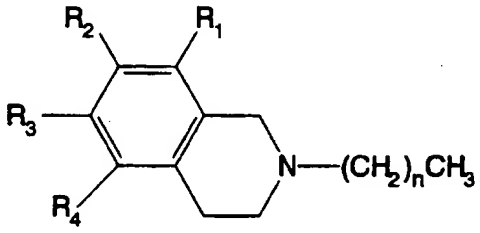


wherein

R_1-R_4 are the same as described for formula Ia; and

Y_1 is alkyl, optionally substituted aryl, hydroxyalkyl, or optionally substituted alkaryl.

Other examples include those having the Formula (*Id*):

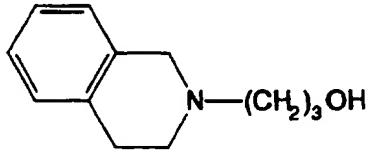


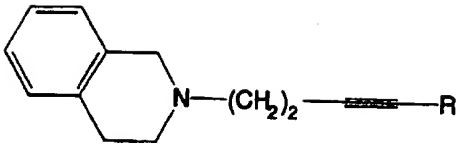
wherein

R_1-R_4 are the same as described for formula Ia; and

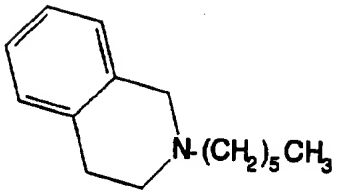
n is 1, 2, 3, 4, 5, or 6.

Particular examples of compounds having Formula *I* include

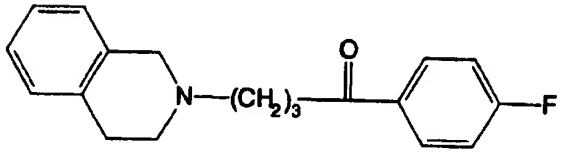




R = H, Ph;



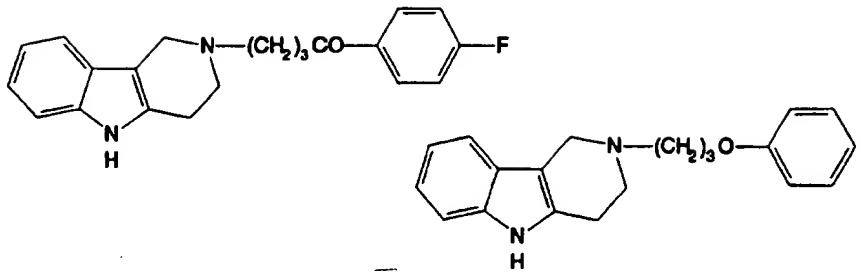
and



Compounds having Formula *II* may be prepared by reaction of an appropriately substituted 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole with an electrophilic reagent as mentioned above. The starting 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indoles may be prepared according to Abou-Gharbia *et al.*, *J. Med. Chem.*, *30*:1818-1823 (1987) and Habert *et al.*, *J. Med. Chem.*, *23*:635-643 (1980).

Particular examples of compounds having Formula *II* include 2-(2-phenoxyethyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole, 2-(3-phenoxypropyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole, 2-(3-phenylpropyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole and 2-(3-hydroxypropy)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b)indole.

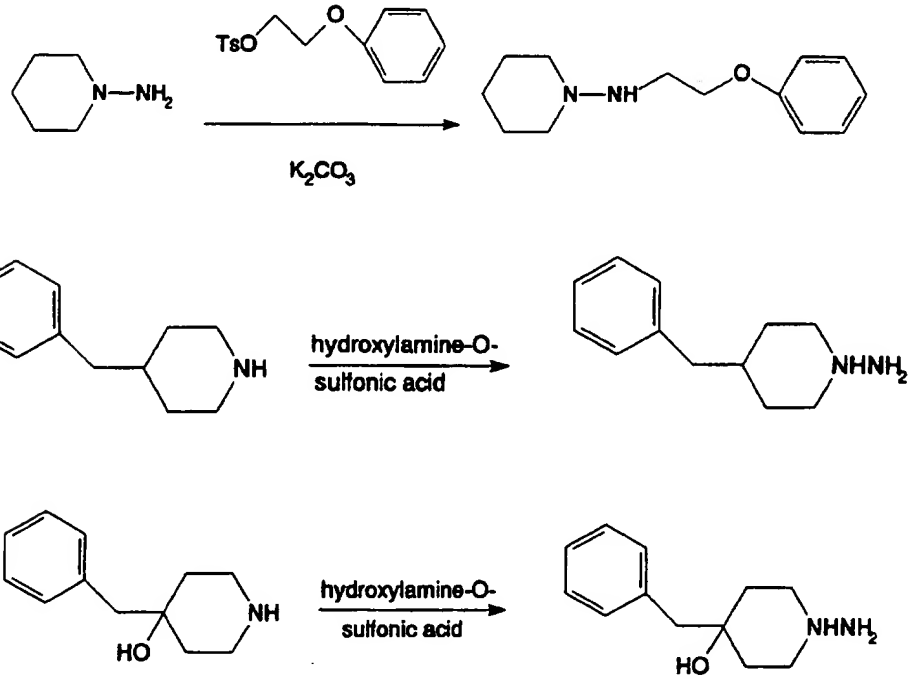
Compounds having Formula *IIa* can be prepared similar to *II*. Particular examples of compounds having Formula *IIa* are



With regard to Formula *III* when p is > 0, then the compounds may exist as a mixture of cis and trans isomers. The invention is directed to such cis and trans isomers as well as the individual enantiomers and diastereomeric mixtures.

When r is zero, G is NH and s is one, the N-amino piperidine compounds may be prepared according to Scheme 1:

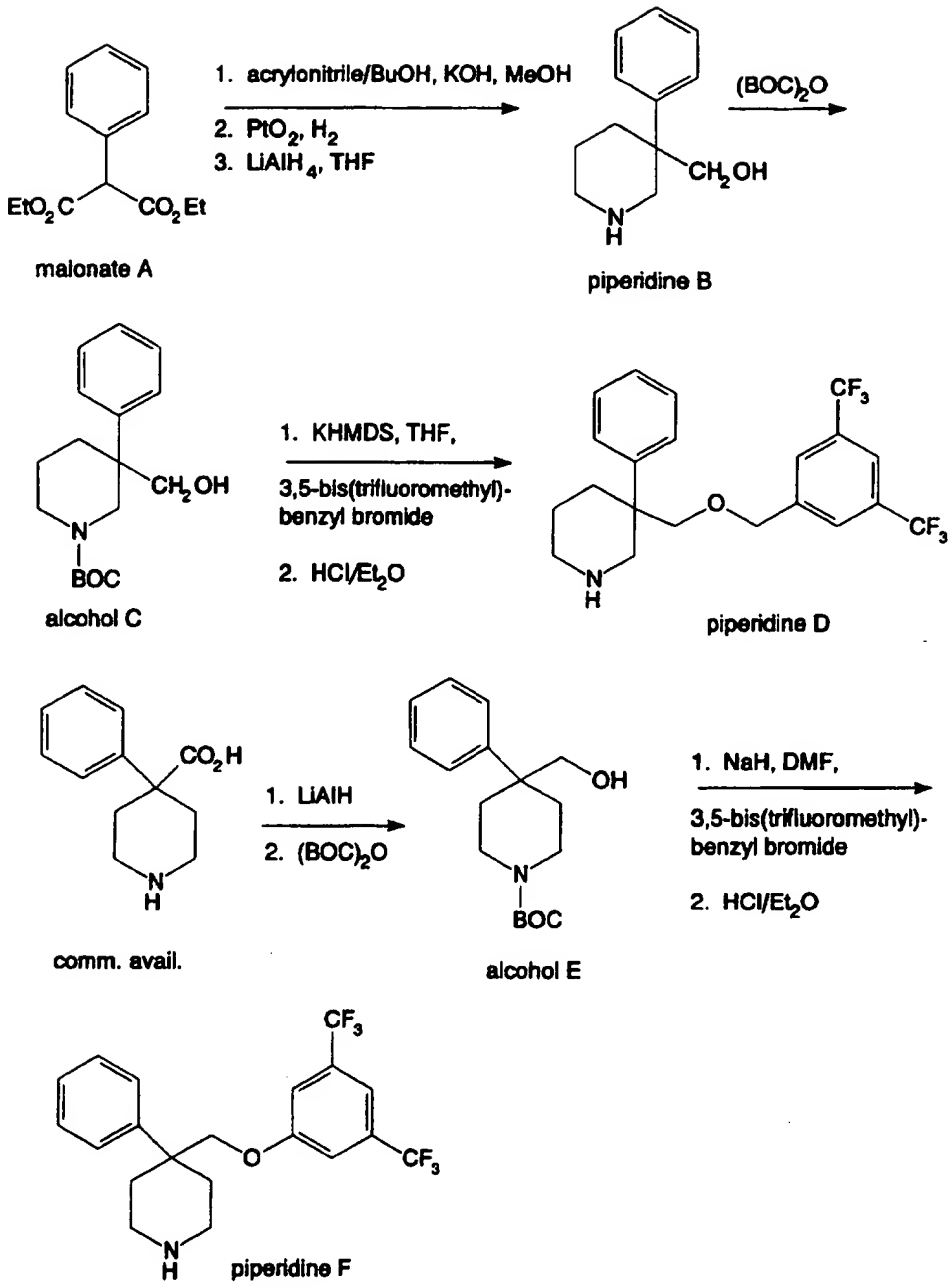
Scheme 1



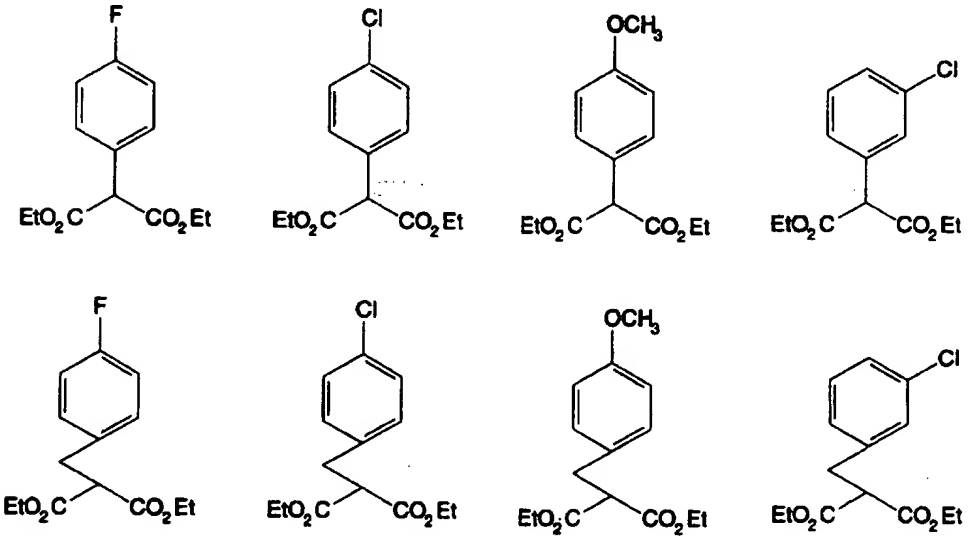
The N-amino piperidines may then be N-alkylated with one of the electrophiles listed above to give the compound of Formula ***III***.

Also with regard to Formula ***III***, when R_1 is an optionally substituted 2-aryloxyalkyl or an optionally substituted 2-benzyloxyalkyl-piperidine, the compounds may be prepared according to Scheme 2:

Scheme 2


1. acrylonitrile/BuOH, KOH, MeOH
2. PtO_2, H_2
3. $LiAlH_4$, THF
$(BOC)_2O$
malonate A
piperidine B
1. KHMDS, THF,
3,5-bis(trifluoromethyl)-benzyl bromide
2. HCl/Et_2O
alcohol C
piperidine D
1. LiAlH
2. $(BOC)_2O$
comm. avail.
alcohol E
1. NaH, DMF,
3,5-bis(trifluoromethyl)-benzyl bromide
2. HCl/Et_2O
piperidine F

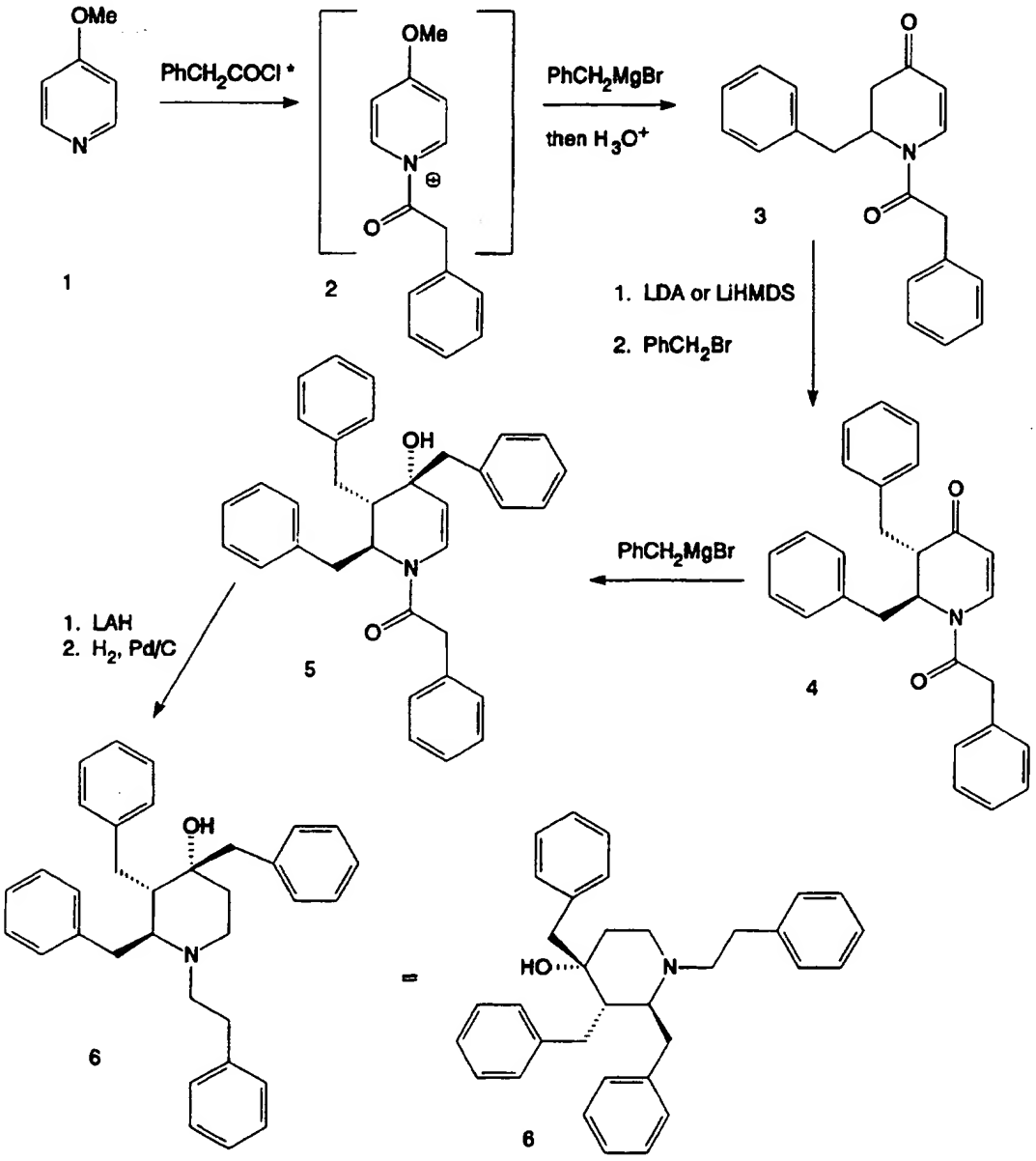
Scheme 2 may be generalized so that malonate A might be any of a variety of aryl or substituted benzyl malonates, for example, those shown below, leading to the corresponding derivatives in the scheme. Each of those piperidines may be alkylated with one or the other of the electrophilic reagents mentioned above.



Scheme 3 depicts a route to some 2-substituted and 2,3-disubstituted-4-benzyl-4-hydroxypiperidines. A variety of electrophilic acylating agents may be used such that the final product **6** may have different substituents on the nitrogen atom. Also note that a variety of Grignard reagents or other nucleophiles can be used in the step **2** → **3** so that the final product **6** may contain various substituents at the 2-position. Also note that a variety of alkylating agents can be used in the step **3** → **4** so that the final product **6** will contain various substituents at the 3-position. Finally, the Grignard reagent in the step **4** → **5** can be used. Also note that a variety of Grignard reagents can be used so that the final product **6** will contain various substituents at the 4-position. Alkylating agents may also include $PhOCH_2Br$ and $PhCH_2OCH_2Br$, for

example. These would introduce oxygen atoms in the substituents at the various positions. Additionally, a high degree of stereocontrol can be achieved with the likely relative stereochemical outcomes shown.

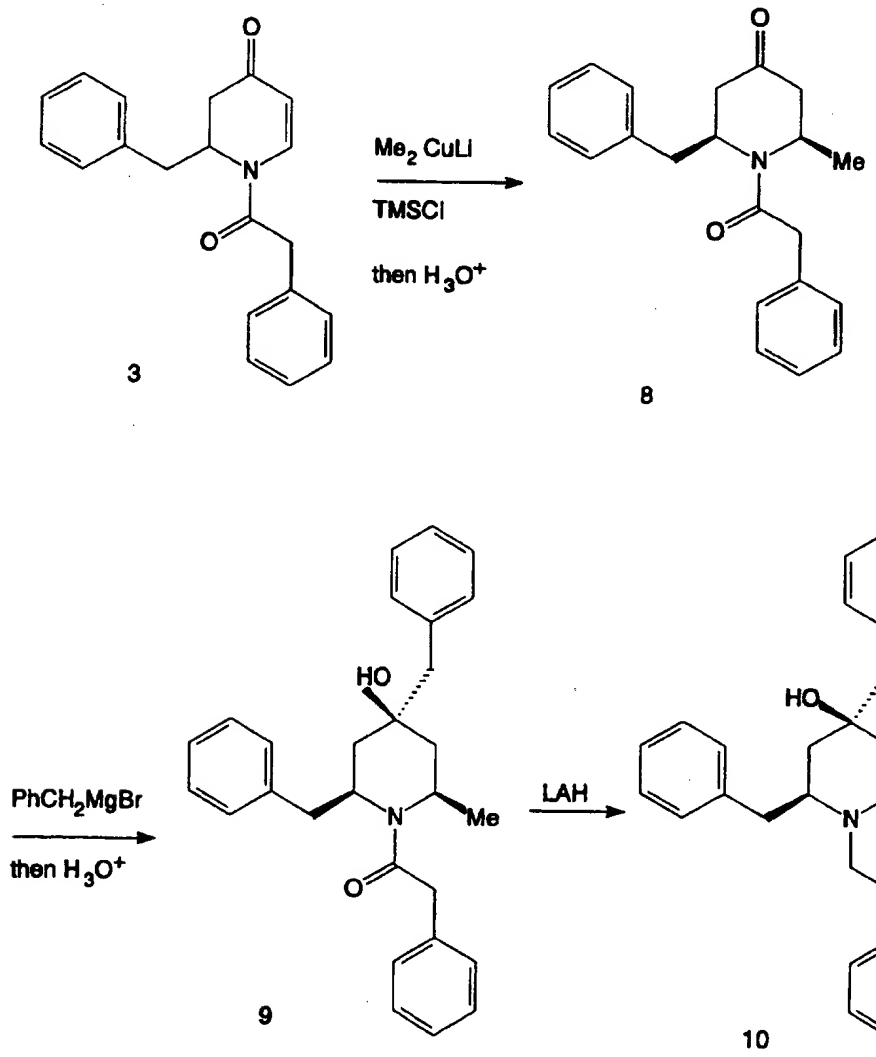
Scheme 3



*Other commercially available electrophilic acylating agents which may be used in the first step of Scheme 3 include $Ph(CH_2)_2COCl$ and $PhOCH_2COCl$.

Other variations of this versatile synthetic approach are also possible (*See*, Scheme 4). Again, the benzyl group was originally introduced as a Grignard reagent so that can be varied (see **2** → **3** above). The cuprate reagent can be varied as well as the final benzyl Grignard reagent. The net result of this chemistry is the preparation of 2,4,4,6-tetrasubstituted N-alkylpiperidines.

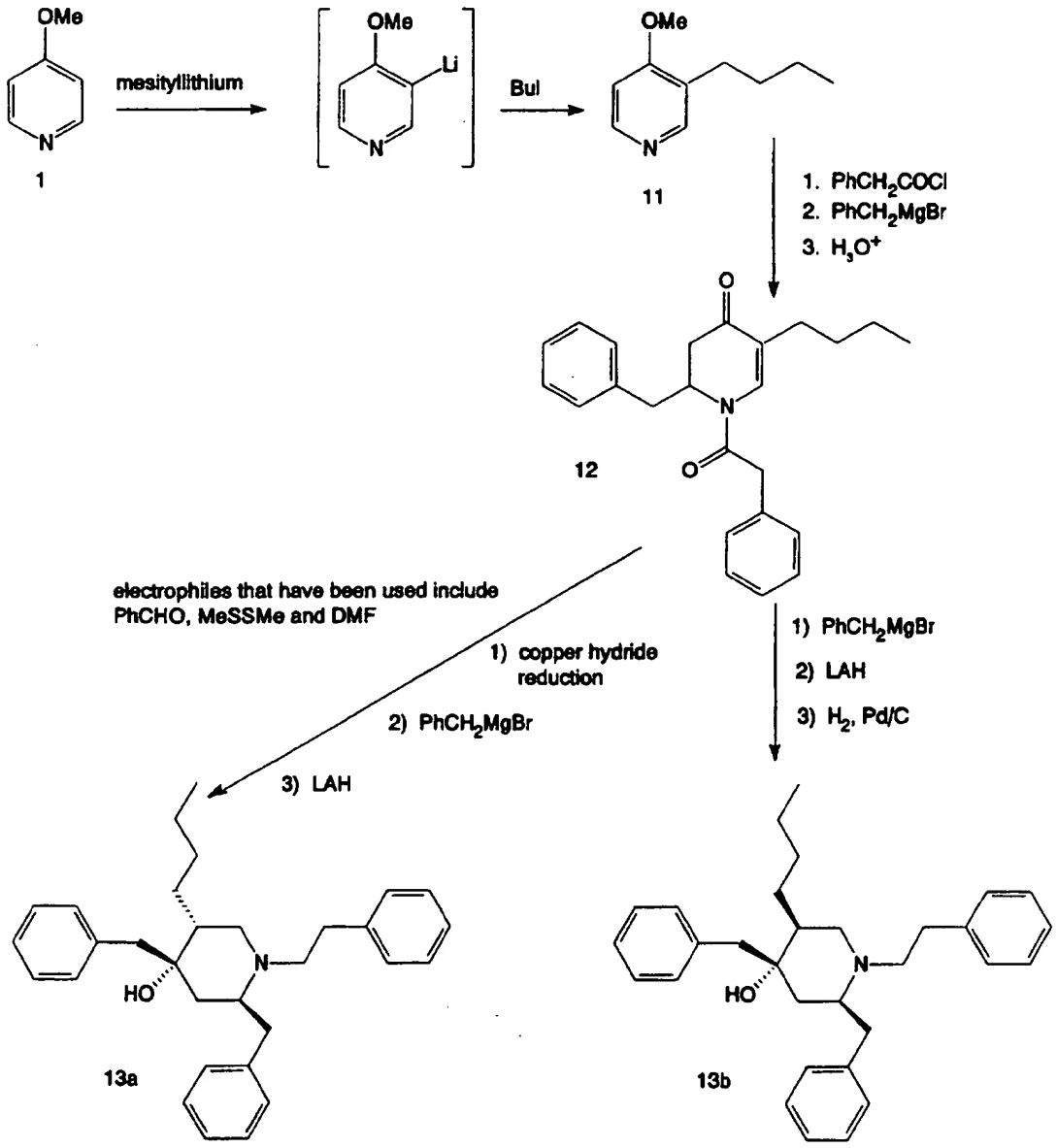
Scheme 4



One can also take advantage of the ortho lithiation of methoxy pyridines described by Comins, D. L., *et al.*,

Tetrahedron Lett. 29 (1988). Routes to novel piperidines are illustrated in Scheme 5 below.

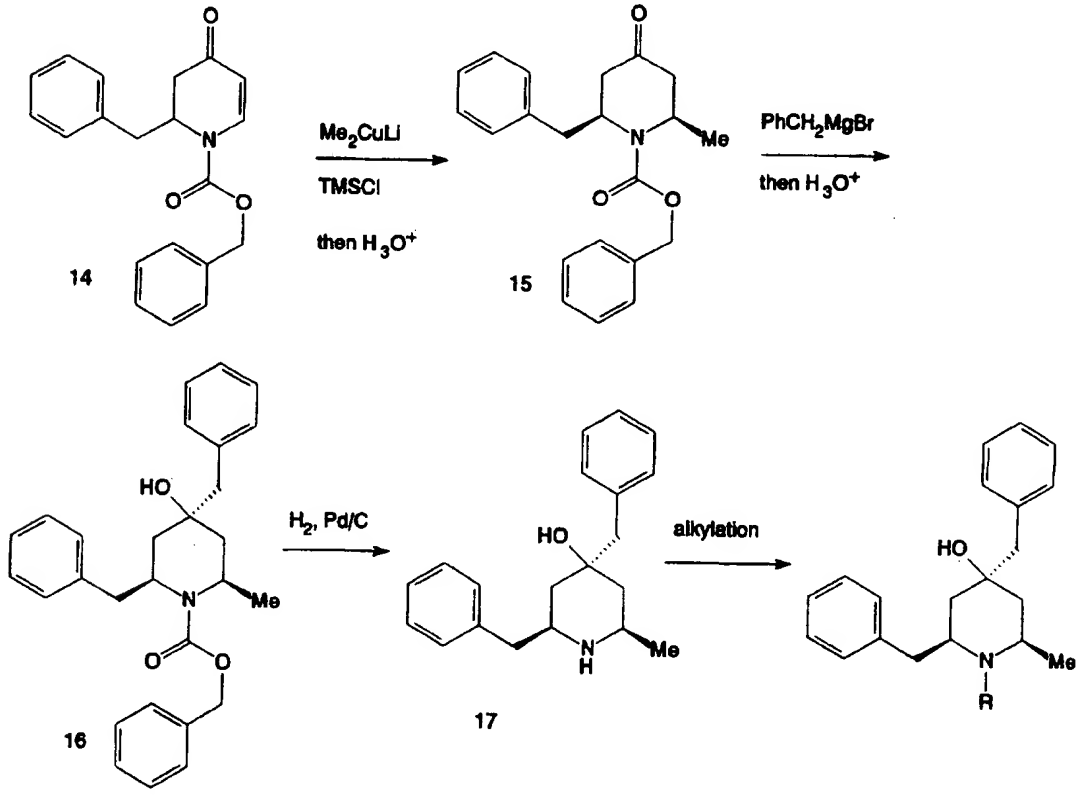
Scheme 5



By choosing benzyl chloroformate as the initial electrophilic N-acylating agent, one can prepare a family of piperidines without a substituent on the nitrogen atom (Scheme 6). N-Phenoxycarbamates can be removed by catalytic hydrogenation with PtO_2 in ethanol (see Comins, D.L. *et al.*, *Tet. Lett. 32*:5697 (1991)).

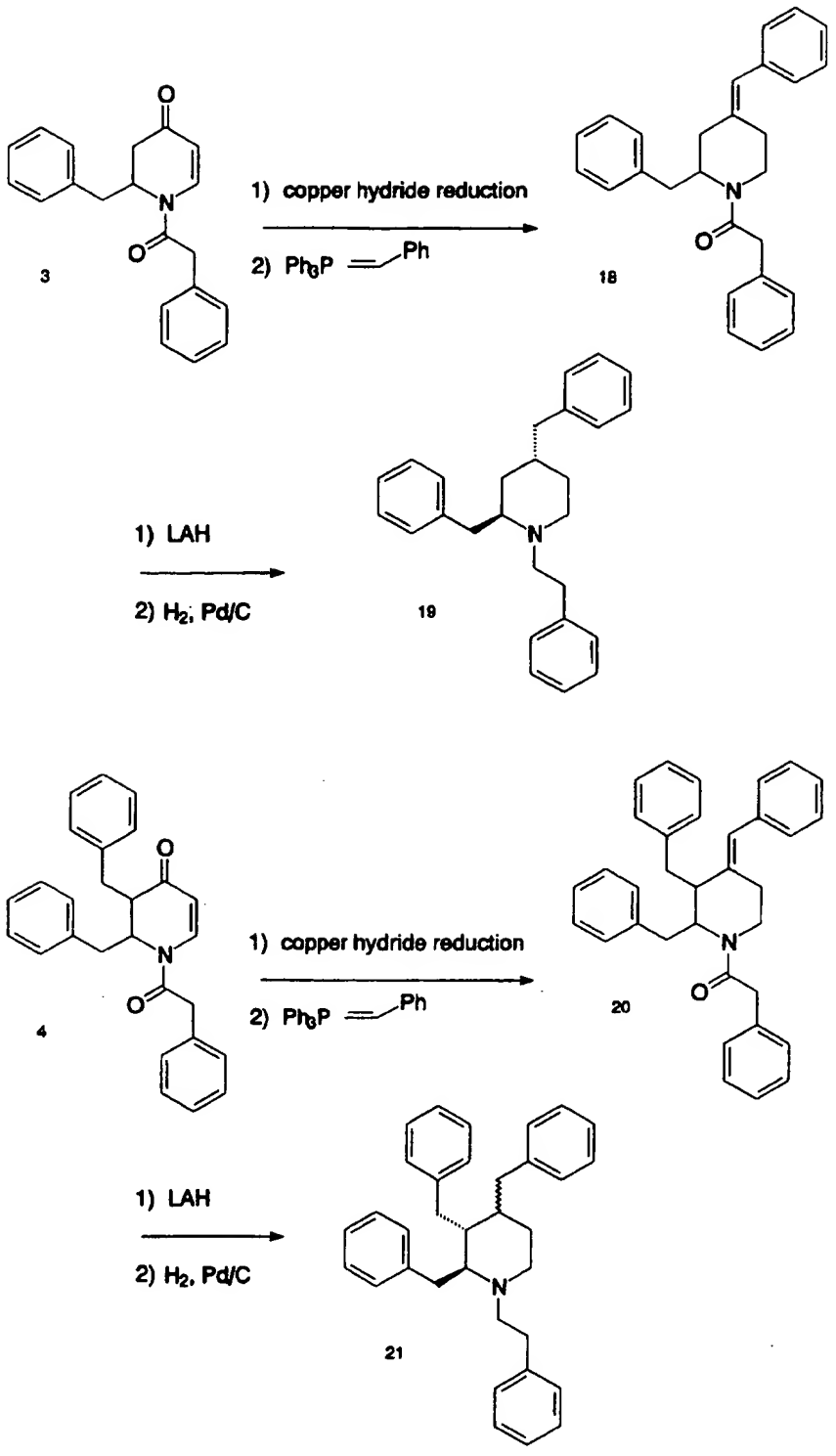
Carbamates formed from other chloroformates can be removed from 2,3-dihydro-4-pyridones by treatment with bases such as sodium methoxide in methanol under reflux. Then, the electrophilic reagents mentioned above may be used to alkylate these piperidine nitrogens. Also note that a variety of electrophilic reagents can be used so that the final products **13** will contain various substituents at the 5-position.

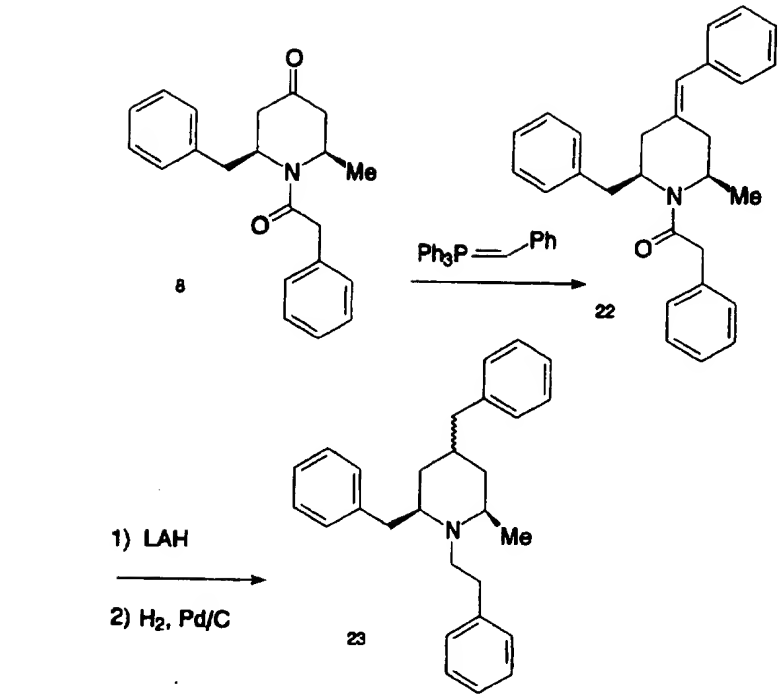
Scheme 6

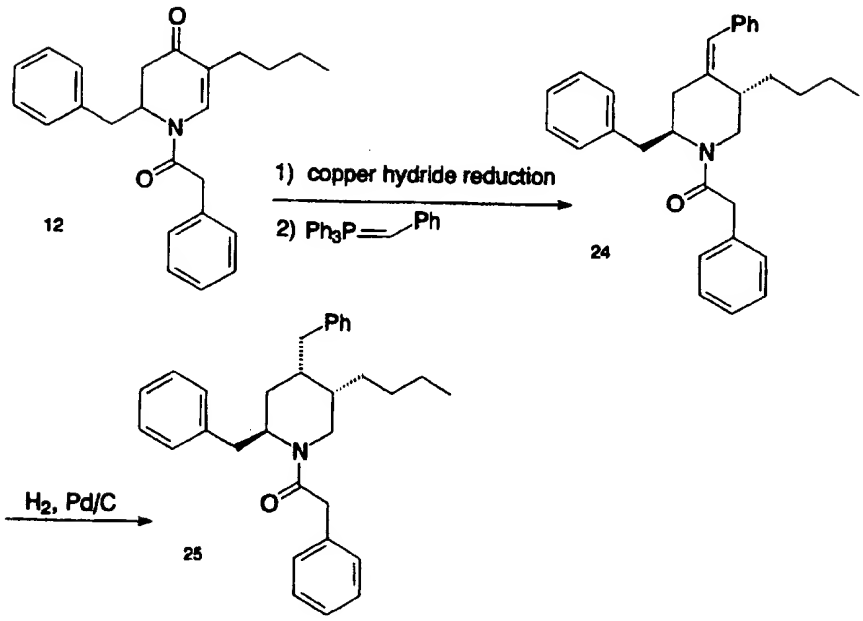


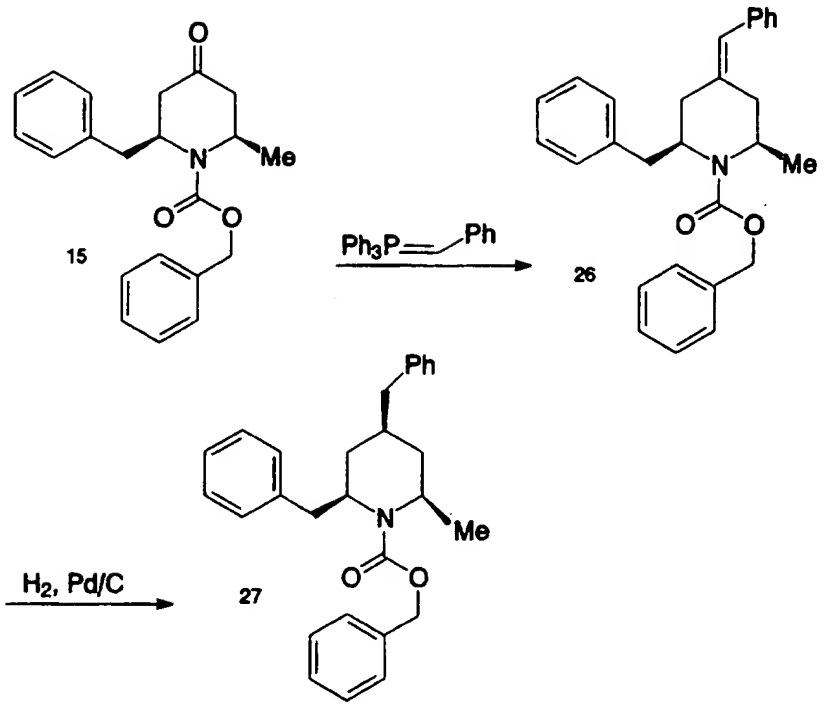
All of the above combinations can be readily made without the hydroxy substituent at C-4 of the piperidine as shown below via Wittig olefination of the piperidone followed by reduction (Scheme 7).

Scheme 7


1) copper hydride reduction
2) Ph3P =Ph
3
18
1) LAH
2) H2, Pd/C
19
1) copper hydride reduction
2) Ph3P =Ph
4
20
1) LAH
2) H2, Pd/C
21


O
N
Me
O
8
Ph_3P=
Ph
22
1) LAH
2) H_2, Pd/C
23

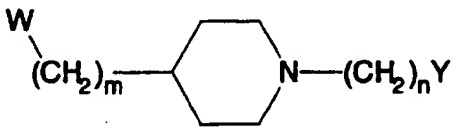

O
N
O
12
1) copper hydride reduction
2) Ph_3P=
Ph
24
Ph
H_2, Pd/C
25



In the transformations of **20** to **21** and **22** to **23**, stereocontrol of the hydride reductions may be achieved by substituting other hydride reagents in place of LAH.

See, Comins, D. L., *et al.*, *J. Org. Chem.* *55*:2574 (1990), Comins, D. L., *et al.*, *Tetrahedron Lett.* *29* (1988), and Comins, D. L., *et al.*, *J. Am. Chem. Soc.* *116*:4719 (1994).

An example of compounds having Formula ***III*** include those having Formula ***IIIa***:



wherein

W is an adamantyl group or an optionally substituted aryl group;

Y is CH_3, CN, CO_2R, carboxamido, an optionally substituted cycloalkyl group or an optionally substituted heterocycloalkyl group;

R is alkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

m is 0, 1, 2, 3;

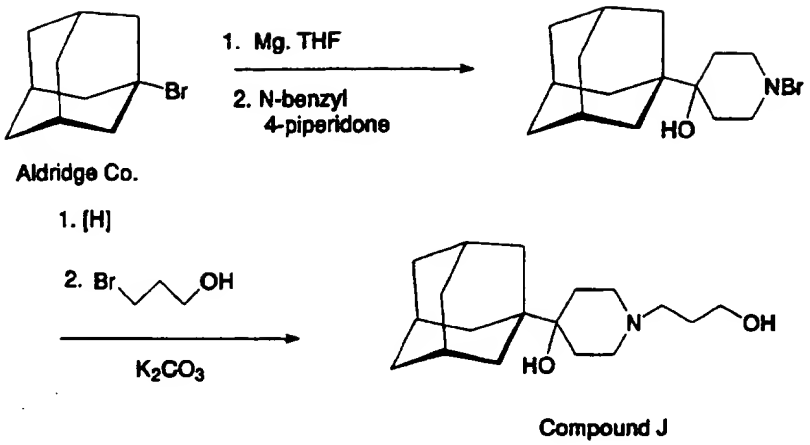
with the proviso, that when W is adamantyl, then Y may also be optionally substituted aryl, optionally substituted aryloxy, SAr, COAr, hydroxy, $=Y_1$, $-Y_1$, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group; wherein

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

Generally, when Y is an aminoalkyl or guanidinoalkyl, n must be greater than 1.

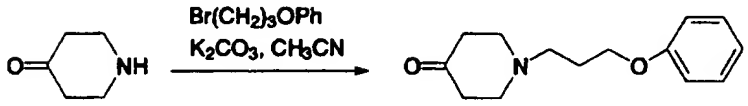
In general, compounds having Formula ***III*** may be prepared by reaction of an appropriately substituted piperidine with one of the electrophilic reagents mentioned above. Where W is an adamantyl group, the compounds may be prepared as shown in Scheme 8. Preferably, such adamantyl groups are 1-adamantyl.

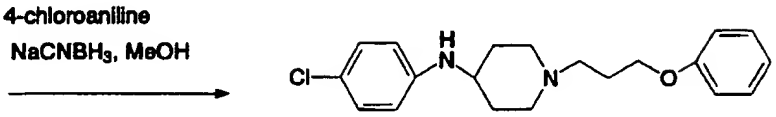
Scheme 8



Compound J

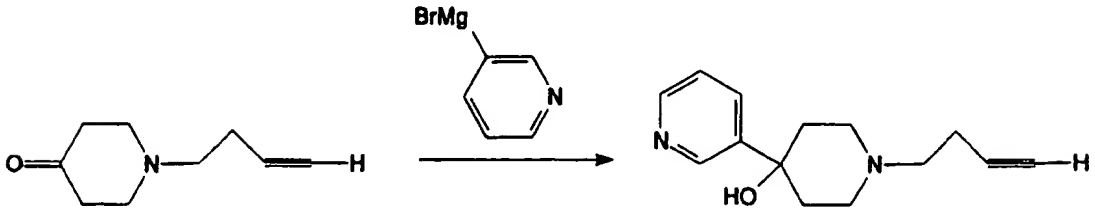
or:





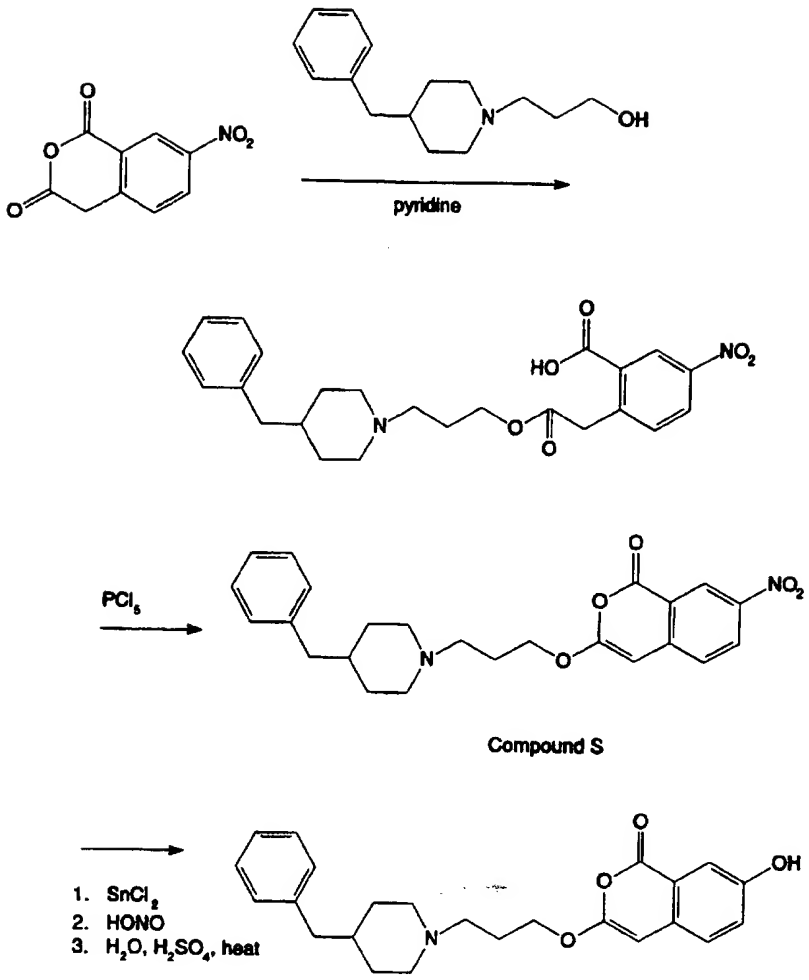
Where W is a heteroaryl group, the compounds may be prepared using an aryl lithium or grignard reagent as shown in Scheme 9.

Scheme 9



Where Y is a 7-substituted isocoumarin, the compounds may be prepared as set forth in Scheme 10.

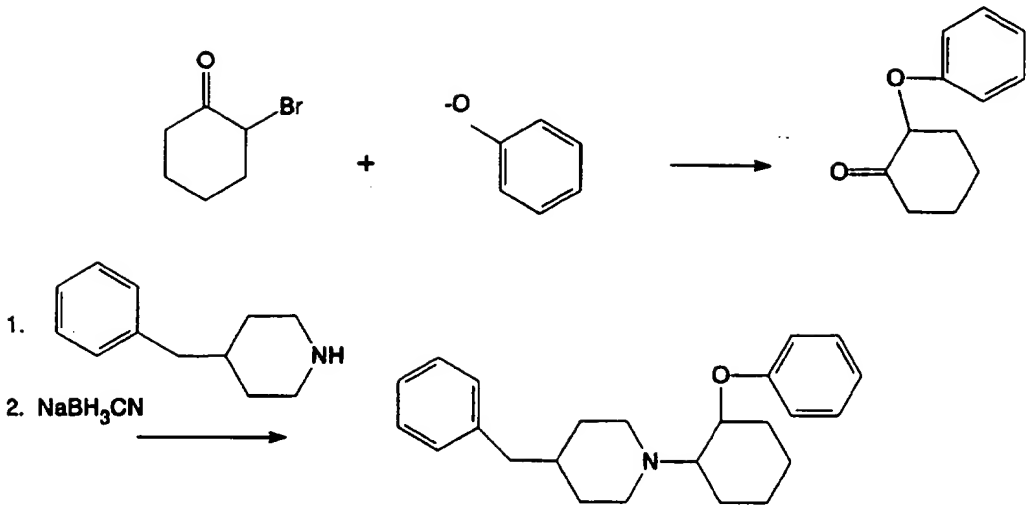
Scheme 10



See, Kerrigan *et al.*, *J. Med. Chem.* *38*:544 (1995) for methods of making such 7-substituted isocoumarins wherein the 7-substituent may be an amino group, a nitro group, or amido group.

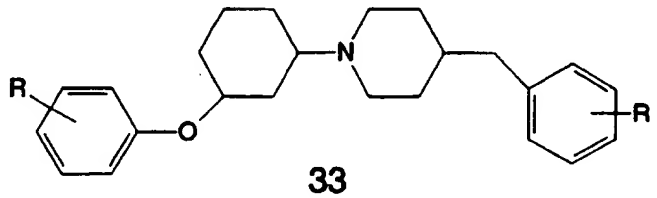
Where Y is an optionally substituted cycloalkyl group or optionally substituted heterocycloalkyl group, and r, s and t are 0, the compounds may be prepared as shown in Scheme 11.

Scheme 11

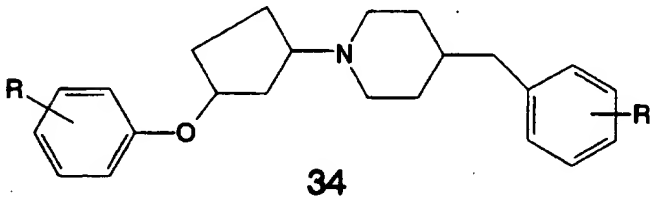


25

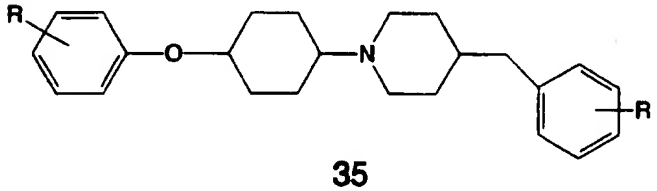
Other cyclized analogs include compounds such as 33-36.



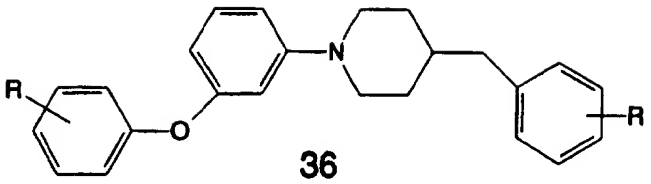
33



34

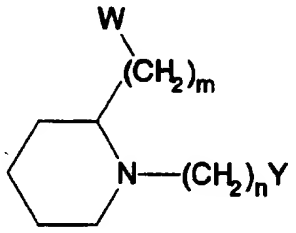


35



36

Another example of compounds within the scope of Formula ***III*** includes compounds having the Formula ***IIIb***:



wherein

W is an adamantyl group or an optionally substituted aryl group;

Y is CH_3, CN, CO_2R, carboxamido, an optionally substituted cycloalkyl group or an optionally substituted heterocycloalkyl group;

R is alkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

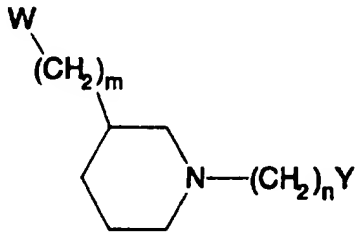
m is 0, 1, 2, or 3;

with the proviso, that when W is adamantyl, then Y may also be optionally substituted aryl, optionally substituted aryloxy, SAr, COAr, hydroxy, $=Y_1$, $-Y_1$, a heterocyclic group, a heteroaryl group, a cycloalkyl

group, an amino group, an amido group, a ureido group, or a guanidino group; wherein

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

Another example includes compounds having the Formula ***IIIc***:



wherein

W is an adamantyl group or an optionally substituted aryl group;

Y is CH_3, CN, CO_2R, carboxamido, an optionally substituted cycloalkyl group, an optionally substituted heterocycloalkyl group, optionally substituted aryl, optionally substituted aryloxy, SAr, COAr, hydroxy, $=Y_1$, $-Y_1$, a heterocyclic group, a heteroaryl group, an amino group, an amido group, a ureidoalkyl group, a guanidinoalkyl group, or $O-N=CR_1R_2$, where R_1 and R_2 are independently aryl or lower alkyl;

R is alkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted

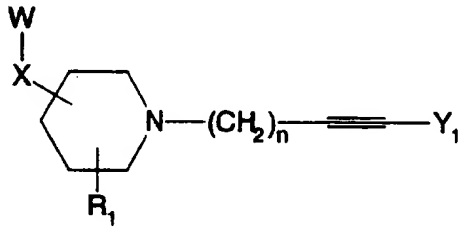
aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guinidinoalkyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

m is 0, 1, 2, or 3;
with the proviso, that when W is adamantyl, then Y may also be optionally substituted aryl, optionally substituted aryloxy, SAr, COAr, hydroxy, $=Y_1$, $-Y_1$, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group; wherein

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

Another example includes compounds having the Formula ***IIId***:



wherein

W is an adamantyl group or an optionally substituted aryl group;

X is a bond, $(CH_2)_m$, oxygen, or NR;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, halo, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

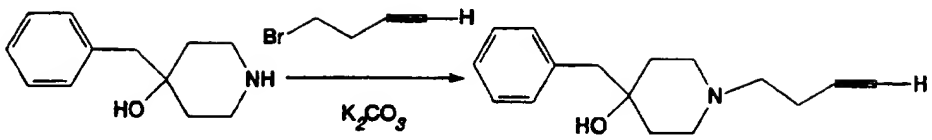
n is 0, 1, 2, 3, 4, 5, or 6; and

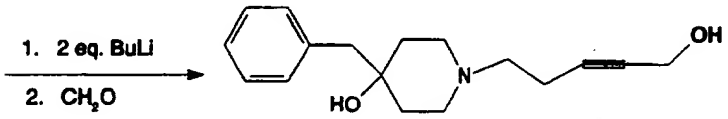
m is 0, 1, 2, or 3;

with the proviso that when W is an adamantyl group, then Y_1 may further be an optionally substituted aralkyl group, or an optionally substituted aryl group.

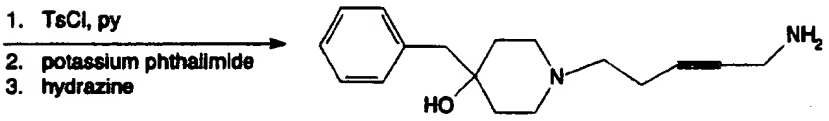
Where the compounds having Formula ***IIId*** terminate with an alkyne (Y_1 = hydrogen), a propargylalcohol (Y = hydroxyalkyl), or propargylamine (Y_1 = aminoalkyl) residue, they may be prepared according to Scheme 12.

Scheme 12



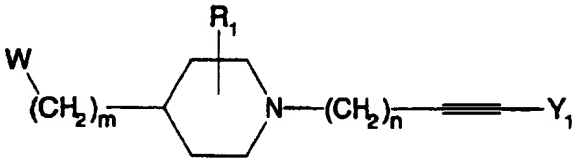


Compound AE



Compound AF

Another example includes compounds having the Formula ***IIIe***:



wherein

W is an adamantyl group or an optionally substituted aryl group;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

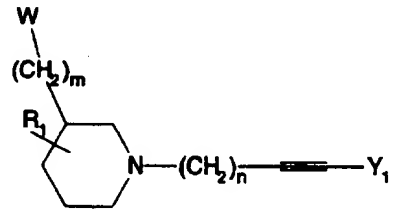
R_1 is hydrogen, hydroxy, halo, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

m is 0, 1, 2, or 3;

with the proviso that when W is an adamantyl group, then Y_1 may further be an optionally substituted aralkyl group, or an optionally substituted aryl group.

Another example includes compounds having the Formula ***IIIf***:

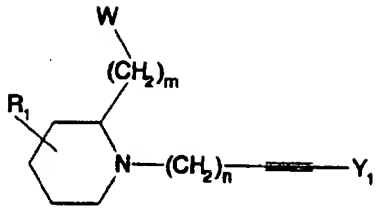


wherein

W, Y_1, R_1, n and m are the same as described in Formula IIIe;

with the proviso that when W is an adamantyl group, then Y_1 may further be an optionally substituted aralkyl group, or an optionally substituted aryl group.

Another example includes compounds having the Formula ***IIIg***:

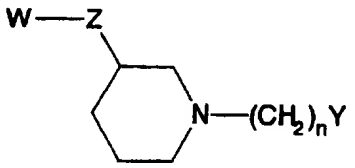


wherein

W, Y_1, R_1, n and m are the same as described in Formula IIIe;

with the proviso that when W is an adamantyl group, then Y_1 may further be an optionally substituted aralkyl group, or an optionally substituted aryl group.

Another example includes compounds having the Formula ***IIIh***:



wherein

W is an adamantyl group or an optionally substituted aryl group;

Y is optionally substituted aryl, optionally substituted aryloxy, SAr, COAr, hydroxy, $=Y_1$, $-Y_1$, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

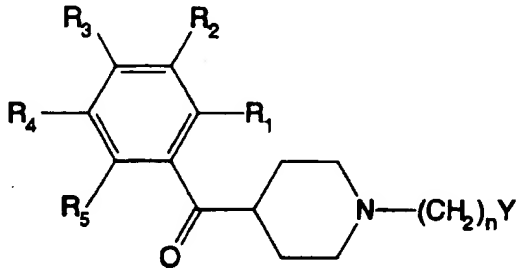
Z is $(CH_2)_m$, oxygen, sulfur, or NR;

m is 0, 1, 2, or 3; and

n is 1, 2, 3, 4, 5, or 6.

Examples of compounds having Formula ***IIIh*** include 3-benzyl-1-(3-phenoxypropyl)piperidine, 3-benzyl-1-(2-phenoxyethyl)piperidine, 3-benzyl-1-(2-phenethyl)piperidine, 3-benzyl-1-[2-(3-trifluoromethyl)phenethyl]piperidine, 3-benzyl-1-[2-(4-aminophenyl)ethyl]piperidine, 3-benzyl-1-[2-(4-chlorophenyl)-ethyl]piperidine, 3-benzyl-1-[2-(4-fluorophenyl)ethyl]piperidine, and 3-benzyl-1-[2-(4-methoxyphenyl)ethyl]piperidine.

Another example includes compounds having the Formula (***IIIi***):



wherein

R_1-R_5 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano,

acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

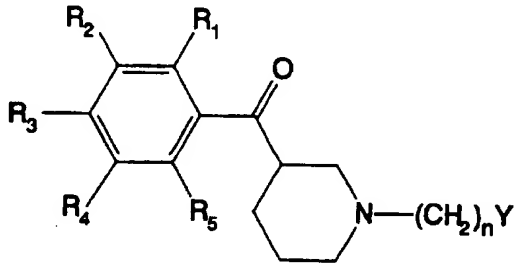
n is 1, 2, 3, 4, 5, or 6;

Y is optionally substituted aryl, optionally substituted aryloxy, SAr, COAr, hydrogen, hydroxy, $=Y_1$, $-Y_1$, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

Compounds having Formula ***IIIi*** may be prepared by reaction of the 4-benzoylpiperidine with one of the electrophiles listed above.

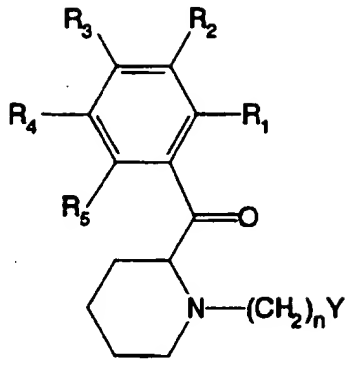
Another example includes compounds having Formula (***IIIj***):



wherein

R_1-R_5, n, Y and Y_1 are the same as described for formula IIIi.

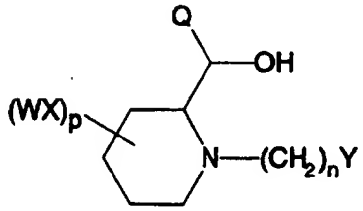
Another example includes compounds having the Formula (***IIIk***):



wherein

R_1-R_5, n, Y and Y_1 are the same as described in formula IIIi.

Another example includes compounds having the Formula (*IIIl*):



wherein

W is optionally substituted aryl;

Y is optionally substituted aryl, optionally substituted aryloxy, an optionally substituted aryloxy group, SAr, COAr, hydrogen, hydroxy, =Y_1, -Y_1, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted

aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

Q is hydrogen, alkyl, aryl, aralkyl, a heterocyclic group, a heterocyclic substituted alkyl group, an aryl group, or an aralkyl group;

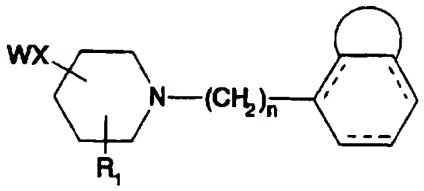
X is a bond, $(CH_2)_m$, oxygen, or sulfur;

m is 0, 1, 2, or 3;

n is 1, 2, 3, 4, 5, or 6; and

p is 0 or 1.

Another example includes compounds having the Formula (***IIIm***):



wherein

W is optionally substituted aryl;

X is a bond, $(CH_2)_m$, oxygen, sulfur, or NR;

R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

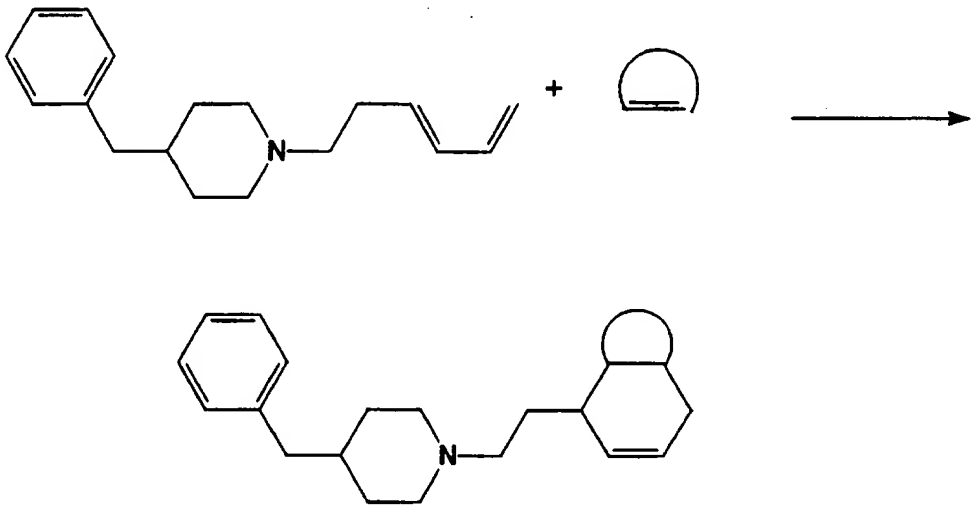
R_1 is hydrogen, hydroxy, aryl, or aralkyl;

n is 1, 2, 3, 4, 5, or 6;

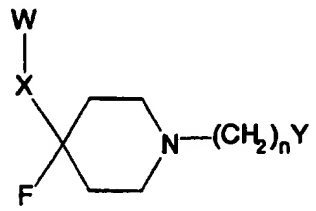
—— - = single or double bond; and

⬡ = carbon ring or heterocyclic ring, with the proviso that said carbon ring is not part of a naphthyl group.

Compounds having Fomula ***IIIm*** may be prepared by a Diels-Alder reaction as shown below:



Another example includes compounds having the Formula (***IIIn***):



wherein

W is an adamantyl group or an optionally substituted aryl group;

X is a bond or $(CH_2)_m$;

Y is CH_3, CN, CO_2R; an optionally substituted aryl group, an optionally substituted aryloxy group, SAr,

COAr, hydroxy, $=Y_1$, $-Y_1$, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group

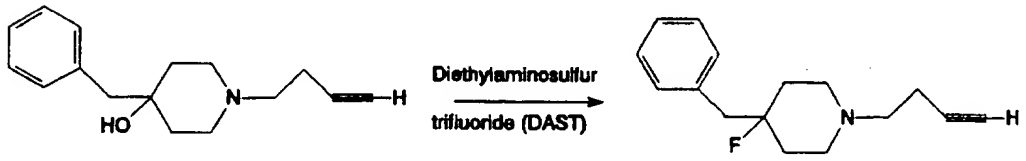
R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

m is 0, 1, 2, or 3.

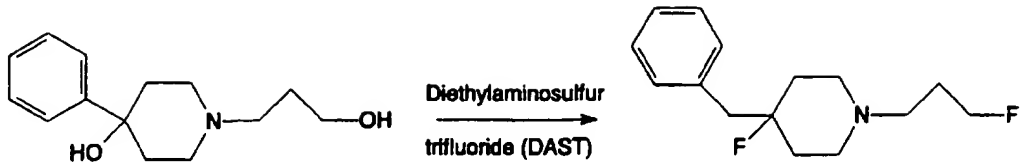
Compounds having Formula ***IIIn***, where the group R_1 is fluoro, may be prepared by reaction of the corresponding hydroxy piperidine with diethylaminosulfur trifluoride as shown in Scheme 13.

Scheme 13



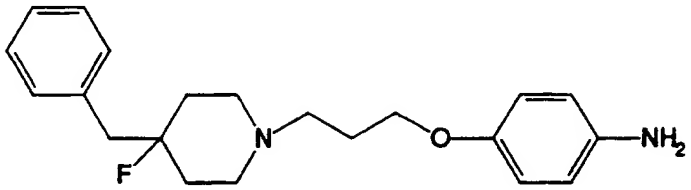
Compound M

See, Sharma, R.A.; Korytnyk, W.; *Tetrahedron Lett* 573 (1977); and Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* 6:183 (1977).

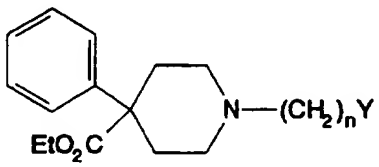


Compound N

An example of compounds having Formula ***IIIn*** includes:



Another example includes compounds having the Formula (***IIIo***):



wherein

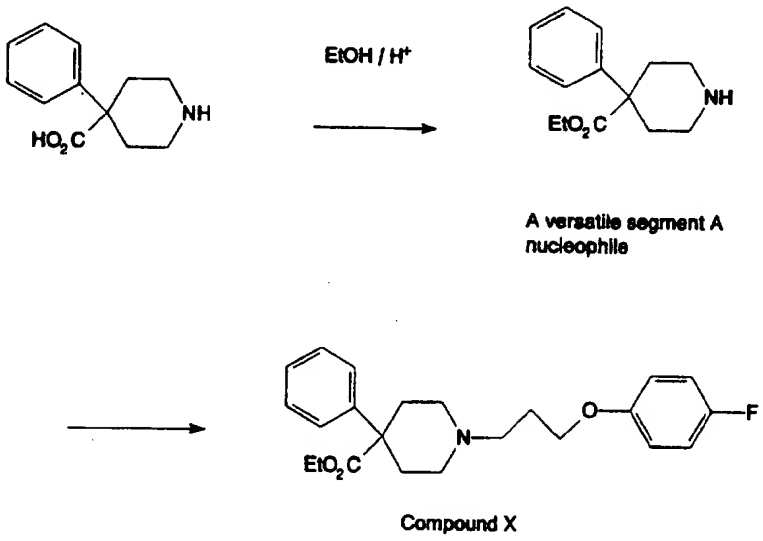
Y is hydrogen, hydroxy, CH_3, CN, CO_2R, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, $=Y_1$, $-Y_1$, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino;

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl; and

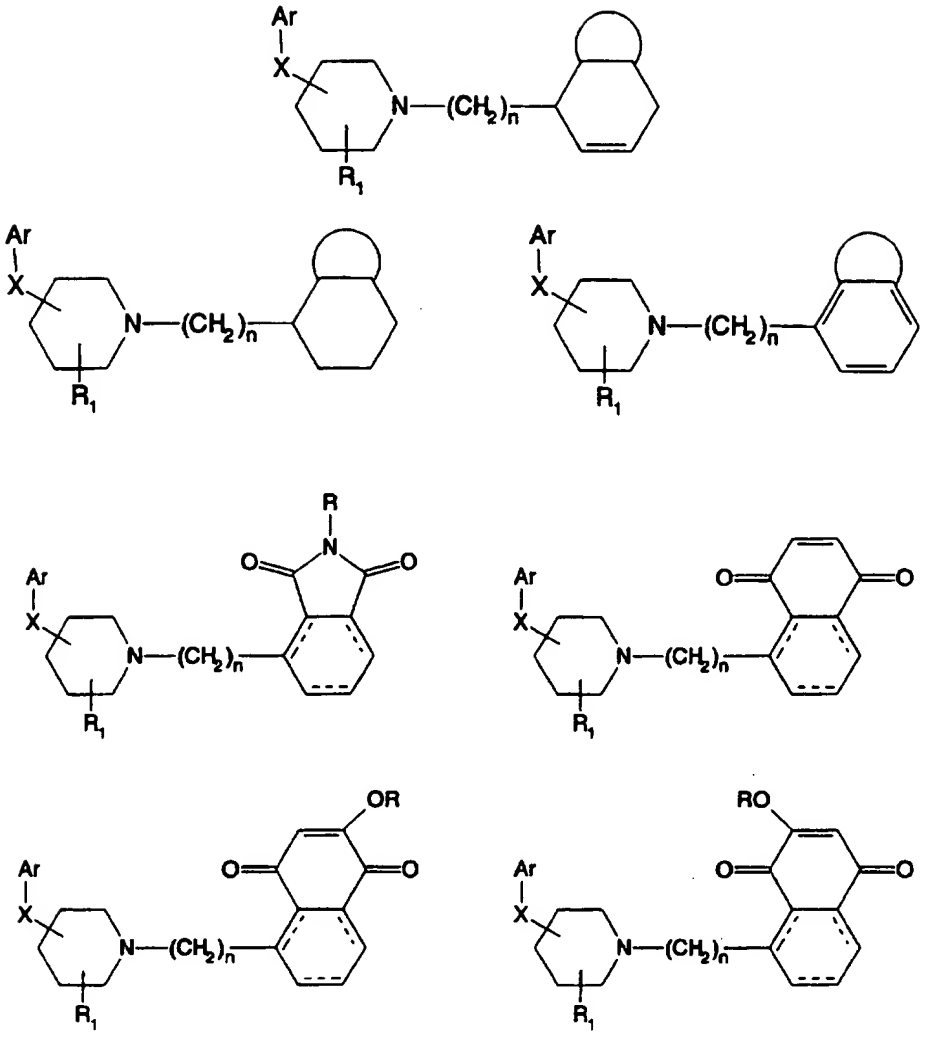
n is 0, 1, 2, 3, 4, 5 or 6.

Compounds having Formula ***IIIo*** may be prepared according to Scheme 14.

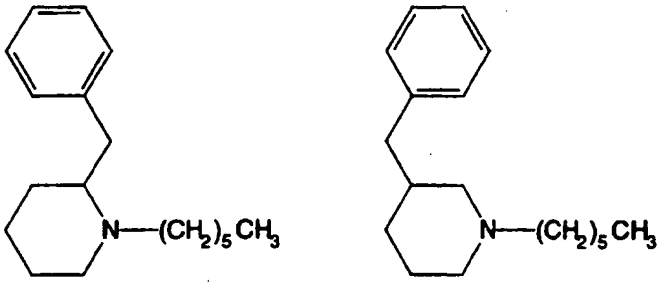
Scheme 14

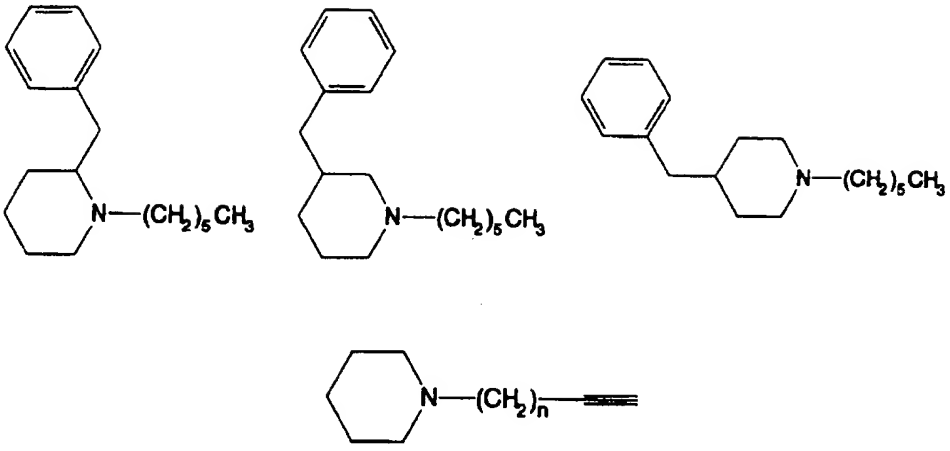


Particular examples of compounds having Formula ***III*** include:

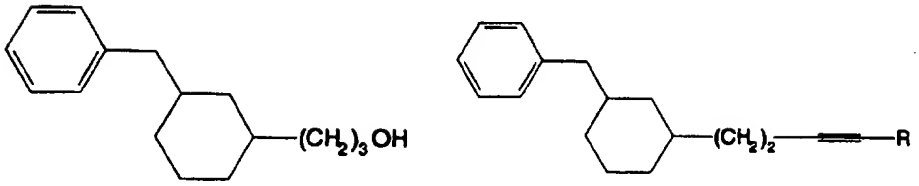


wherein n is 0, 1, 2, 3, 4, 5 or 6;

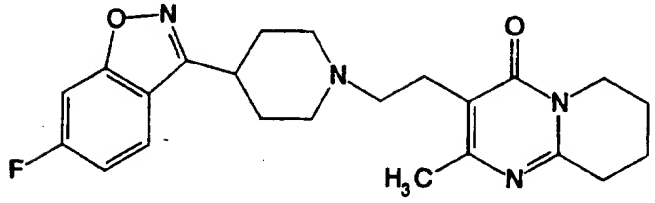


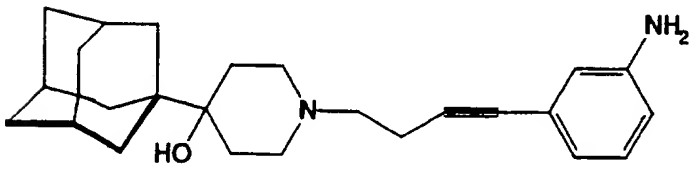


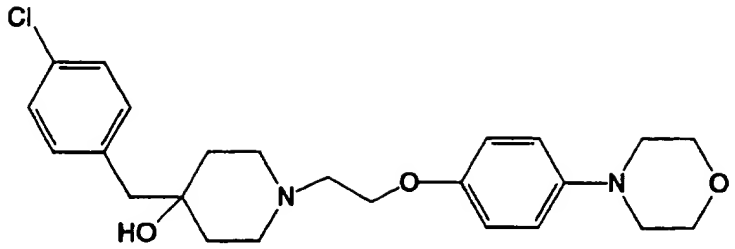
n = 1, 2;

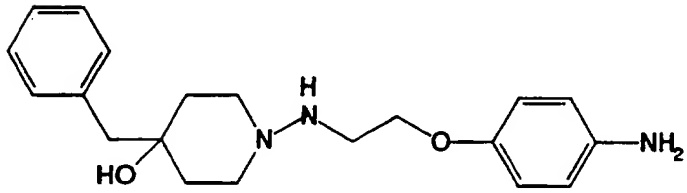


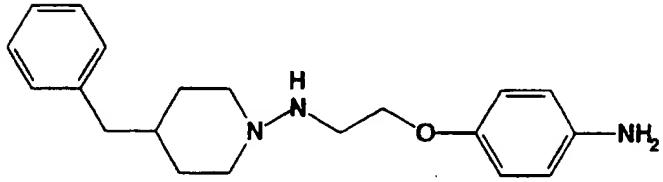
R = hydrogen, aryl;



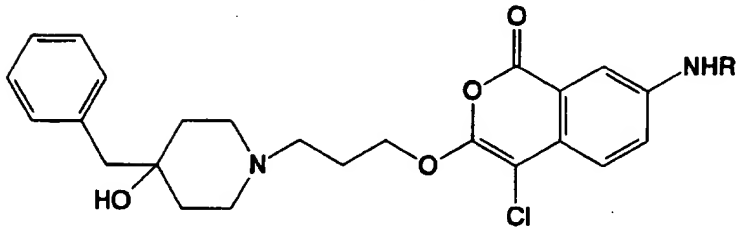




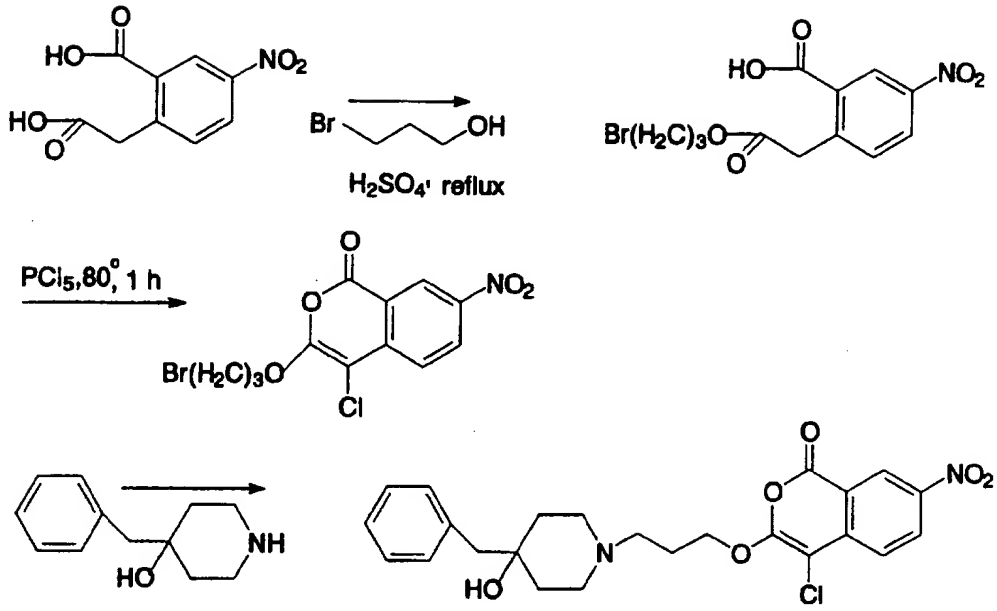




and



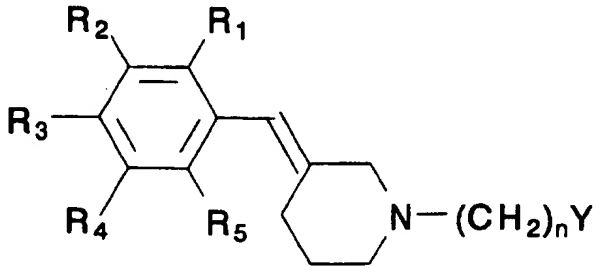
Scheme 15



Method of Harper and Powers, *Biochemistry 24*:7200-7213 (1985).

Additional compounds having Formula ***III*** include 4-benzyl-1-(3-hydroxy-1-methylpropyl)piperidine, 4-benzyl-1-(2-hydroxyethyl)piperidine, 1-benzyl-3-hydroxy-3-phenylpiperidine, 3-hydroxy-3-phenyl-1-phenethylpiperi-dine, 3-hydroxy-3-phenyl-1-(phenylpropyl)piperidine, and 4-benzoyl-1-(3-hydroxypropyl)piperidine.

Examples of compounds having Formula ***IV*** include those having the Formula (***IVa***):



wherein

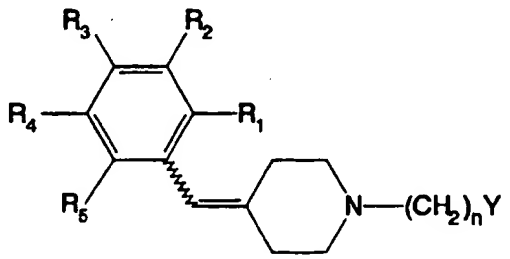
R_1-R_5 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

n is 1, 2, 3, 4, 5, or 6;

Y is optionally substituted aryl, optionally substituted aryloxy, SAr, COAr, hydrogen, hydroxy, $=Y_1$, $=Y_1$, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

Another example includes compounds having the Formula (*IVb*):



wherein

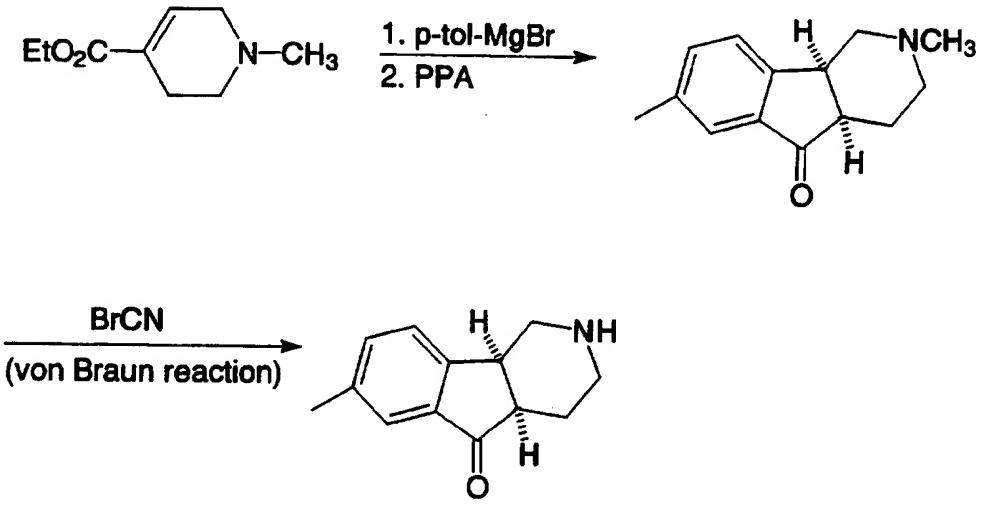
R_1-R_5, n, Y and Y_1 are the same described in formula IVa.

Compounds having Formula ***IV*** may be prepared by reaction of the corresponding piperidone with a Wittig reagent derived from a benzyl bromide. Alternatively, a benzyl grignard reagent may be reacted with the piperidone to give the hydroxybenzyl piperidine which may be dehydrated with sulfuric acid and heat.

Particular examples of compounds having Formula ***IV*** include 1-benzyl-4-(m-fluorobenzylidene)piperidine, 1-(3-hydroxypropyl)-4-benzylidenepiperidine, and 1-hexyl-4-benzylidenepiperidine.

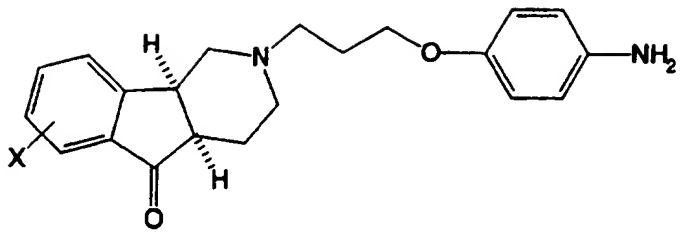
Compounds having Formula ***V*** may be prepared according to Scheme 16 followed by reaction with one of the electrophiles mentioned above.

Scheme 16



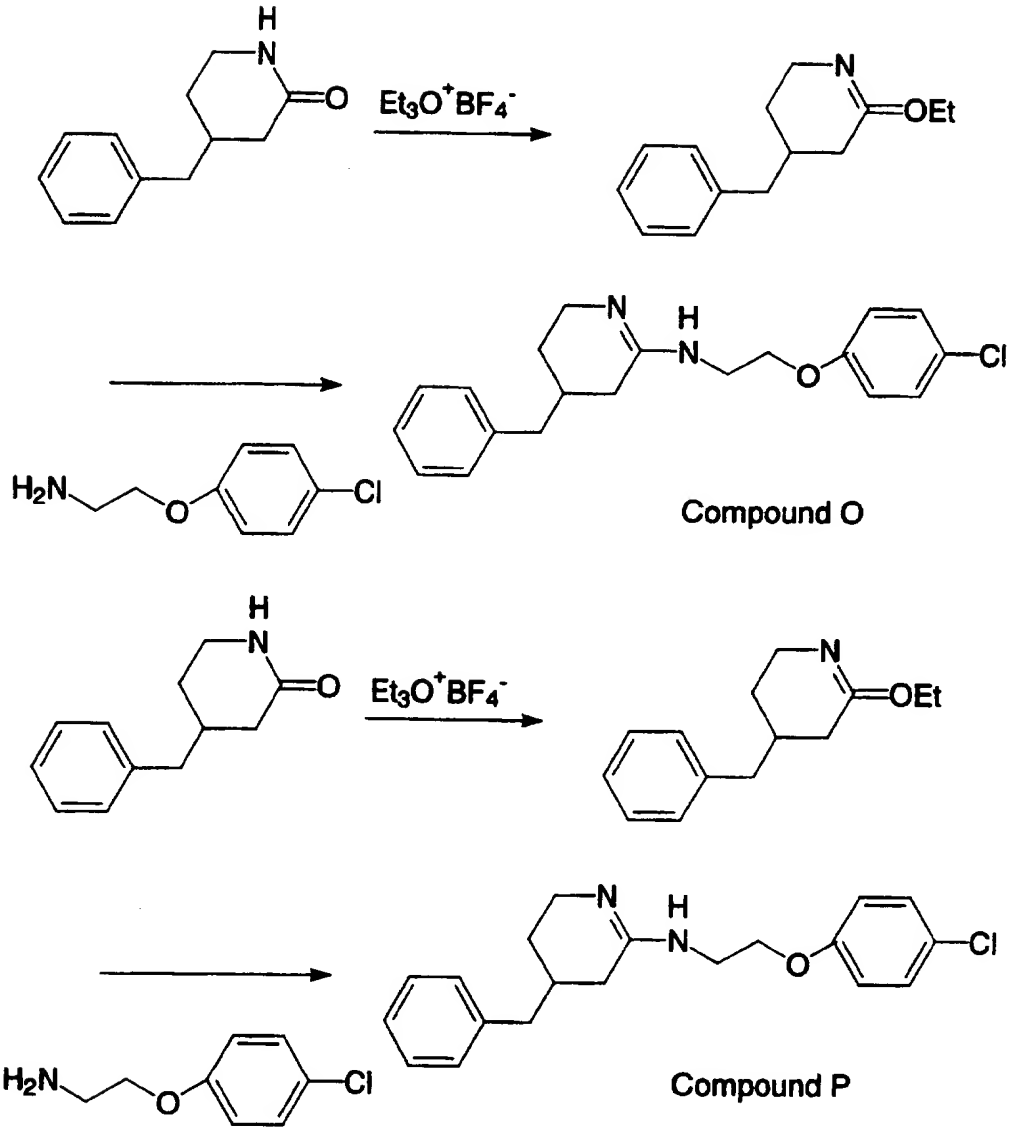
See, Cook *et al.*, *J. Med. Chem.* *38*:754 (1995).

An example of compounds having Formula ***V*** include:

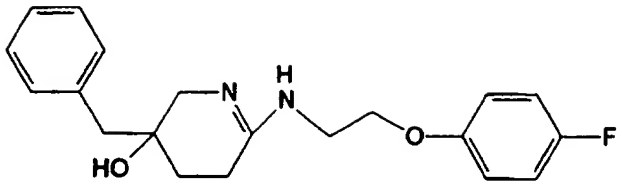


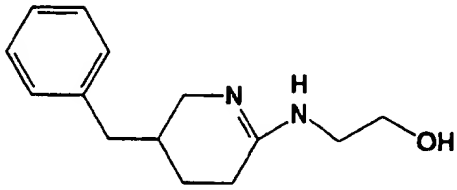
Compounds having Formula *VI* may be prepared according to Scheme 17.

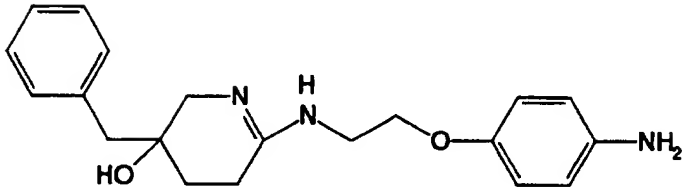
Scheme 17



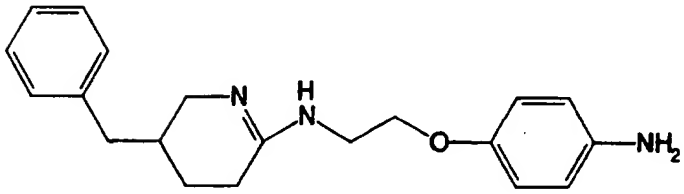
By varying the choice of the amine nucleophile, one can synthesize a family of amidines including the following:





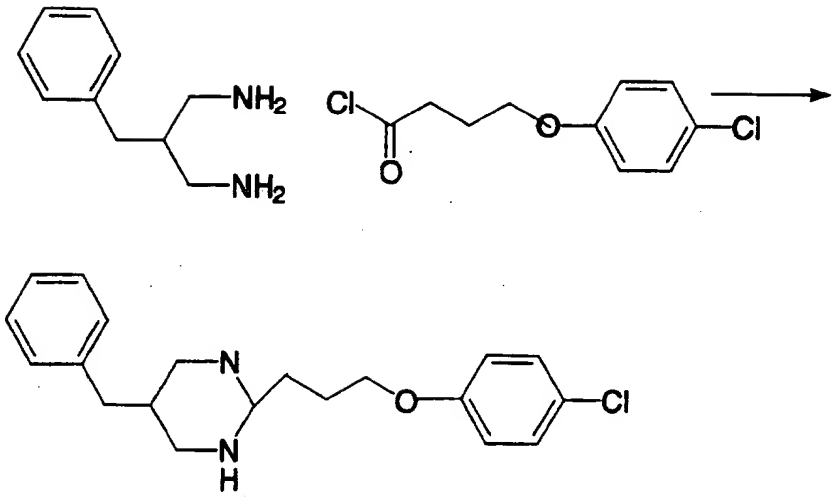


and



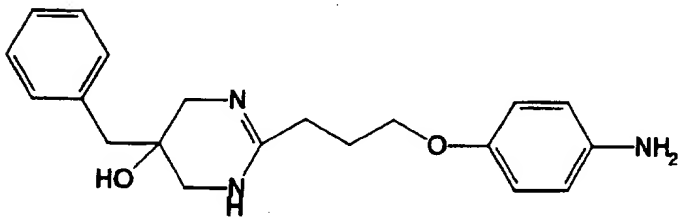
Compounds having Formula ***VII*** may be prepared according to Scheme 18.

Scheme 18

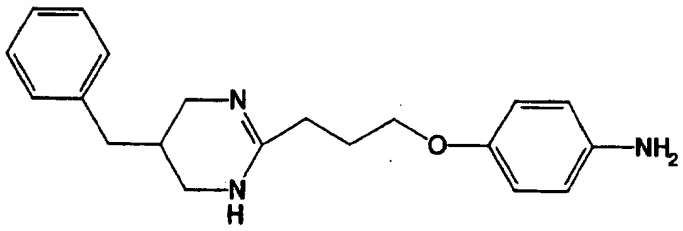


Compound Q

Examples of compounds having Formula ***VII*** include:

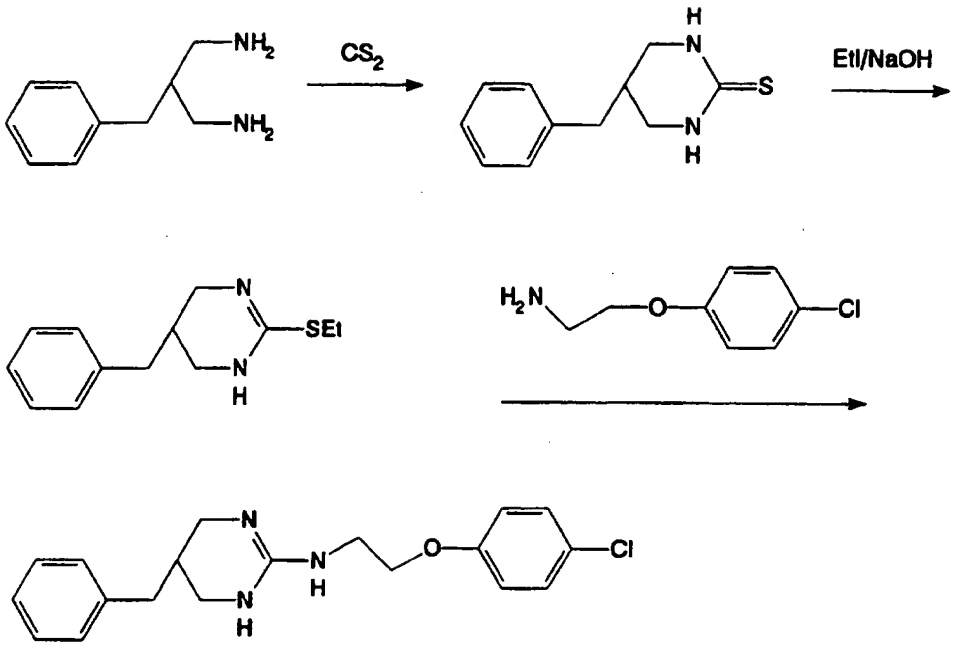


and

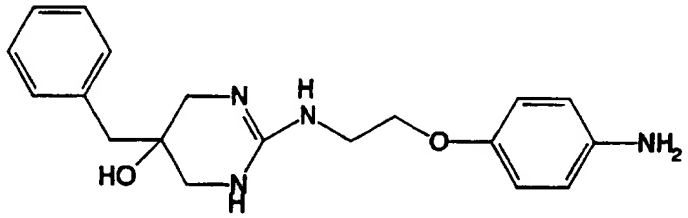


Compounds having Formula ***VIII*** may be prepared according to Scheme 19.

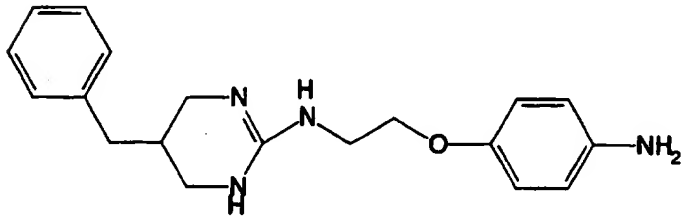
Scheme 19



Examples of compounds having Formula ***VIII*** include:

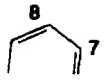


and



Compounds having Formula ***IX*** may be prepared according to Scheme 20.

Scheme 20



ERROR: ioerror
OFFENDING COMMAND: image

OPERAND STACK:
--nostringval--
--nostringval--
--nostringval--
--nostringval--
--nostringval--
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